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Organic Chemistry

Arkivoc **2017**, part iv, 194-209

Synthesis of *cis*-enamide macrocycles via ring-closing metathesis

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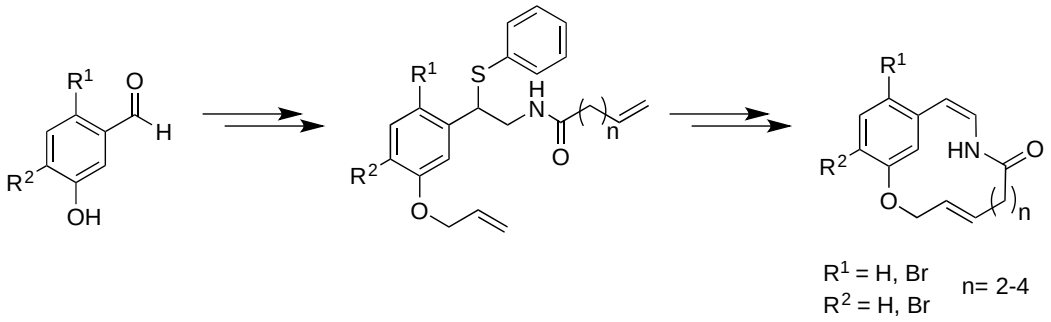
Received 01-12-2017 **Accepted** 02-25-2017 **Published on line** 05-21-2017

Abstract

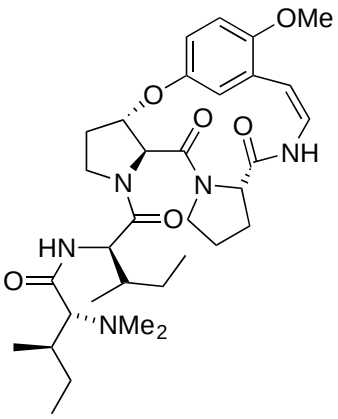
Herein we report the synthesis of 13-, 14- and 15-membered cyclic lactams, using Grubbs' RCM method in 25, 52 and 46% yields respectively. The *cis*-enamide functional group was successfully introduced into these cyclic lactams by *syn* sulfoxide elimination The synthetic cyclic lactams resemble natural cyclic peptides. Our synthetic methodology provides a simple route to making medium-sized cyclic lactams that could be used as models to mimic the β-turn in natural proteins, an important marker in understanding their biological activity.



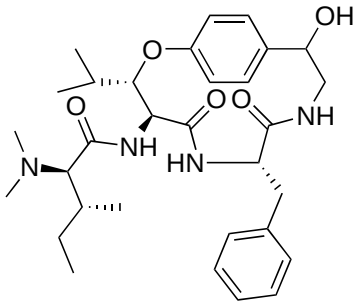
Keywords: cyclopeptide alkaloids, ring closing metathesis, sulfoxide elimination

Introduction

Over the past five decades, about 500 cyclopeptides have been isolated from over 120 species. A large number of 13-, 14- and 15-membered cyclopeptides have been isolated from plants belonging to the Rhamnaceae, Sterculiaceae, Pandaceae, Rubiaceae, Urticaceae, Hymenocardiaceae, and Celastraceae families.[1-6] We are interested in the chemistry of the cyclic lactams with an enamide (styrylamide) functionality in their cyclic structure, e.g. zizyphine A,[7] or a secondary alcohol group, which probably is the precursor to the styrylamide through dehydration, as in pandamine (Figure 1).[8] Plant cyclopeptides have shown various bioactivities, such as antitumor, antibacterial, antifungal, antiHIV, antimalarial, antiplasmodial, insecticidal, antiplatelet, cyclooxygenase and tyrosine inhibiting activities.[9-13]



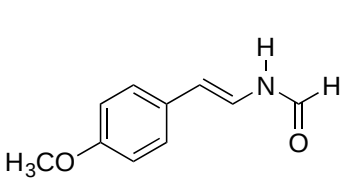
zizyphine A



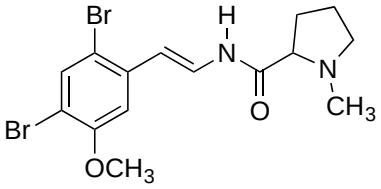
pandamine

Figure 1. Same examples of cyclic peptides.

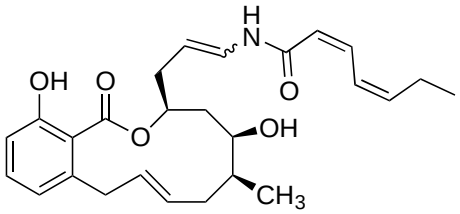
Our interest in the chemistry of enamides (styrylamides) arose from our ongoing program of study of the synthesis and biological activity of acyclic enamides, like tuberine and amathamide A (Figure 2).[14-18] Many of the acyclic enamides isolated from marine sources as ascidians,[19-23] microorganisms,[24-26] fungal and higher plants[27-31] exhibit a variety of pharmacological activities.[25,26,32,33] Especially the macrolides salicylihalamides A and B,[34,35] apicularen A and B[36] and lobatamide A-F[37,38] isolated from marine sponge Haliclona sp., Chondromyces sp. (myxobacteria) and tunicates, respectively. Salicylihalamides A, B and lobatamides are highly potent cytotoxic macrolides, incorporating salicylic acid, a 12-membered lactone ring and an enamide side-chain (*trans* A, *cis* B) (Figure 2).



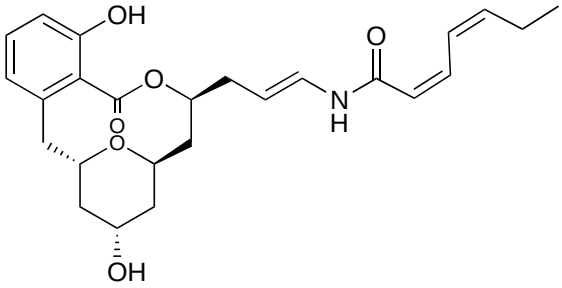
tuberine



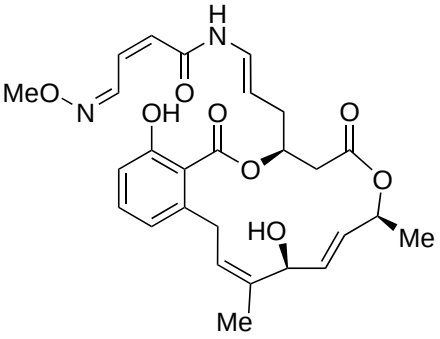
amathamide A



salicylihalamide A: 17E
salicylihalamide B: 17Z



apicularen A



lobatamide A

Figure 2. Some examples of biologically active acyclic enamides.

Salicylihalamide A and lobatamide A display potent cytotoxicity in the NCI 60-cell line human tumor assay, and it is suggested that these compounds may act by a novel mechanism of action.[39] Recently, it has been reported that salicylate enamide macrolides selectively inhibit the Vo sector of the V-ATPase through *N*-acyliminium ion generated from *N*-acyl enamines under acidic conditions.[39] Figure 4 shows how the acyliminium is captured by a nucleophilic amino acid side-chain, and subsequently undergoes irreversible hydrolysis. A study on the structure-activity relationships (SAR) of (-)-salicylihalamide A reported by Barbander and co-workers, revealed that the characteristic *N*-acyl enamine functionality is essential for the biological activity.[40,41,42] This mechanistic route via the enamide ATPase protein interaction, its biological implications, and its stereochemistry attracted our attention and prompted us to develop a simple and efficient synthetic route to the acyclic enamide tuberine and its analogs, in order to study in detail their biological properties.[14-18]

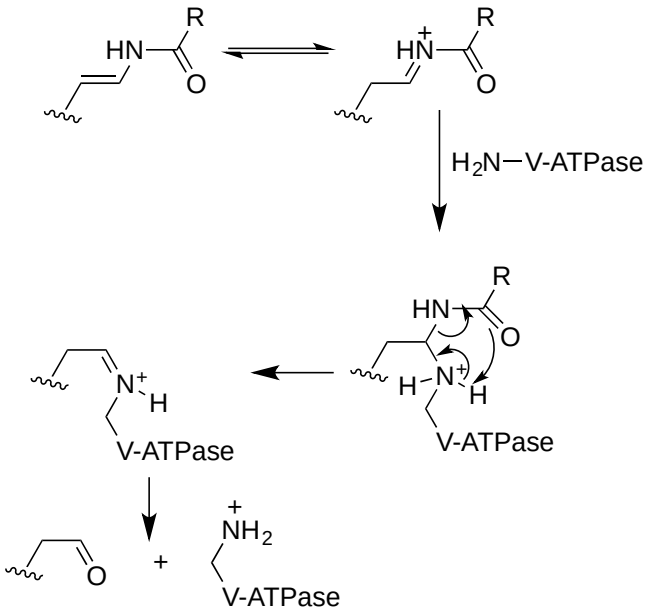


Figure 3. Mechanism of action.

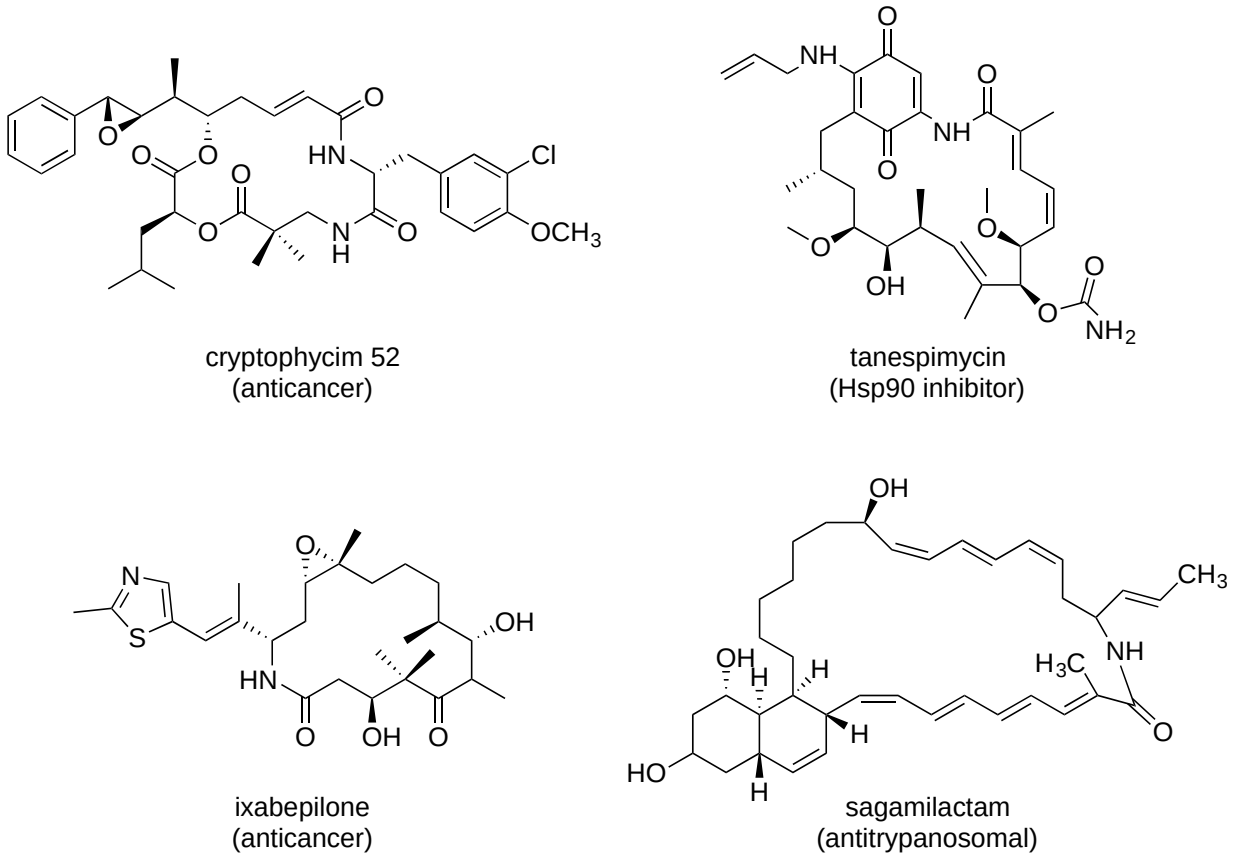


Figure 4. Biologically active macrocyclic lactams and enamides.

Biologically active macrocylic lactams and enamides have been reported, isolated from natural sources. The cryptophycins are a family of highly cytotoxic, cyclic depsipeptides and are among the the most potent agents, and their binding to tubulin is very strong and poorly reversible. Many cryptophycins have been

isolated fron *Cyanobacterium nostoc* sp.[43] Cryptophycin 52 (Figure 4) was produced by total chemical synthesis and it destroys microtubules in vascular smooth muscle cells. Ixabepilone is a semisynthetic epothilone B analogue, which acts like Paclitaxel as a microtubule stabilizing agent. It is used in the treatment of aggresive metastatic or locally advanced breast cancer.[44] Tanespimycin is a derivative of the antibiotic geldanamycin that is being studied in the treatment of cancer, specifically in young patients with certain types of leukemia or solid tumors, especially kidney tumors. It works by inhibiting Hsp90, which is expressed in those tumors, and it belongs to the family of drugs called antitumor antibiotics.[45] Finally, sagamilactam is a polyunsaturated and polyoxygenated macrocyclic lactam containing diene, triene and tetraene conjugated olefins and a decalin moiety which has antitrypanosomal activity.[46]

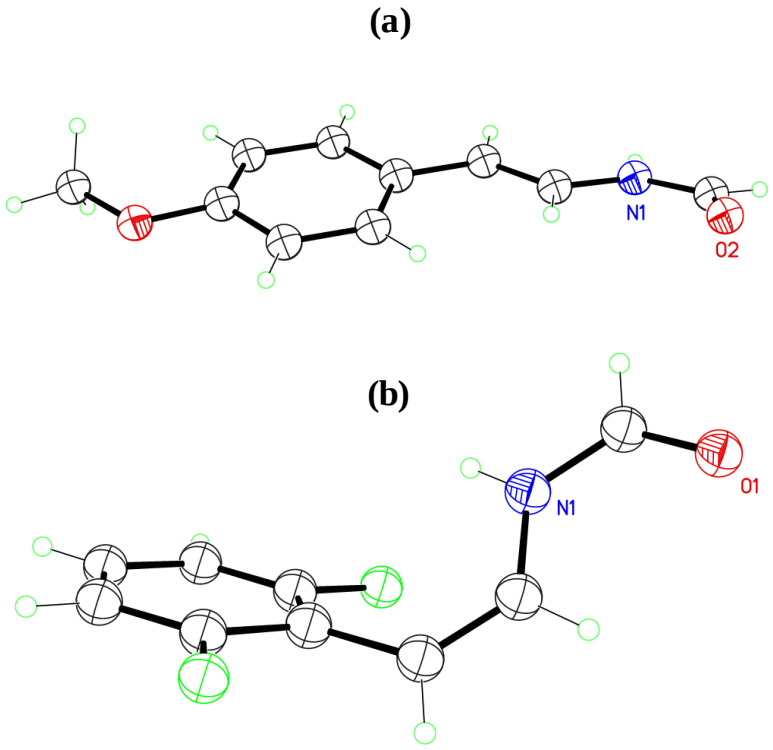


Figure 5. Structure of the *trans*-*N*-(β-4-methoxystyryl)formamide (tuberine) (a) and *cis*-*N*-(β-2,6-difluorostyryl)formamide (b).

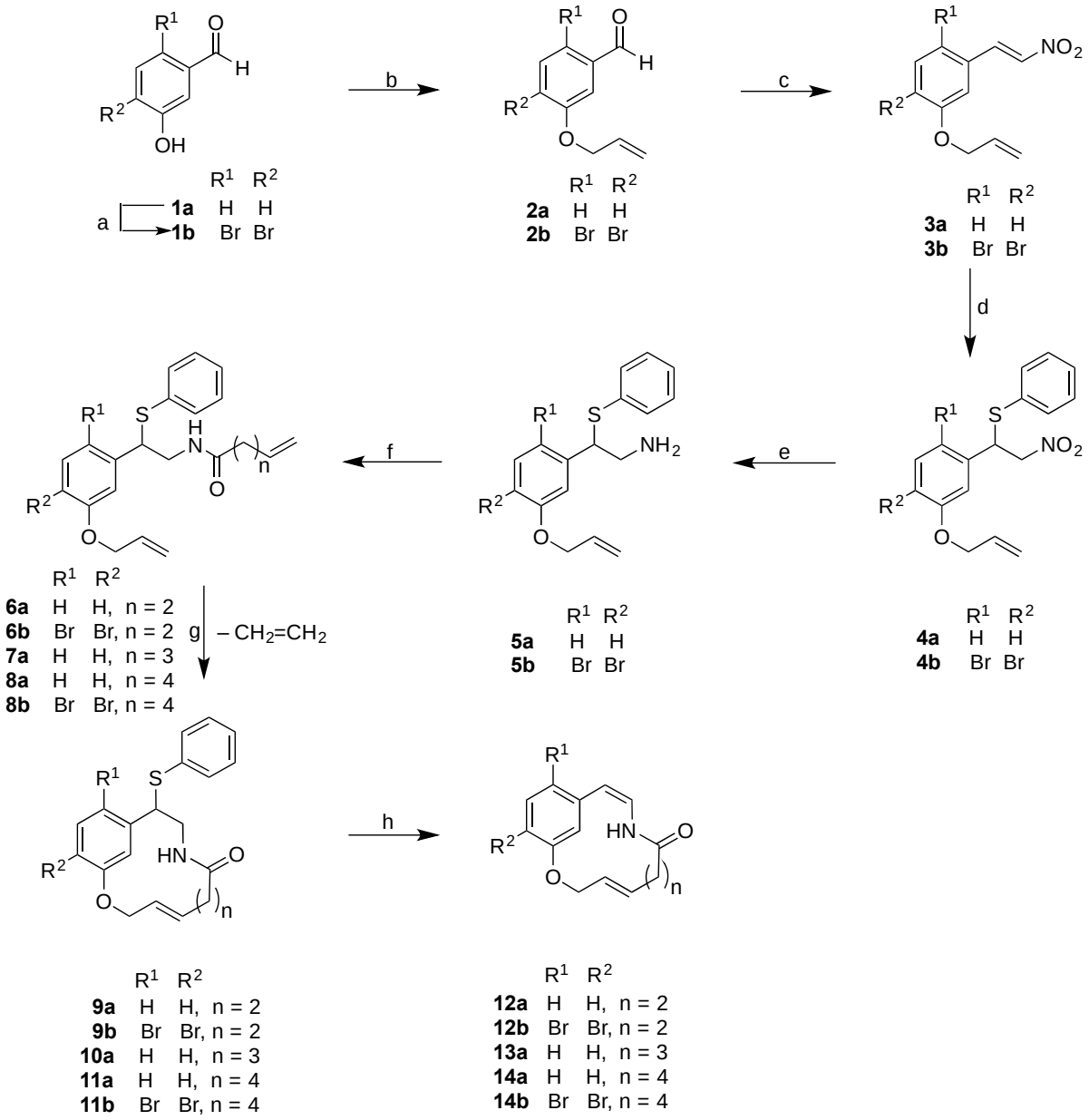
In our synthesis of tuberine and other simple acyclic enamides, the method we used involved thermal *syn*-elimination of β-sulfoxide derived from an amide to generate the enamide functional group.[15-18] This method was successfully employed in the synthesis of some naturally occurring *N*-acylenamides.[16] In most cases when the *N*-acyl is a formyl group, the *Z*-*N*-alkenylformamides were the major product. The naturally occurring tuberine also exhibited a similar *Z*:*E* ratio. In addition, ^{1}H NMR signals for the two stereoisomers due to the conformers arising from restricted amide bond rotation were encountered, which led us to calculate a rotational barrier of 19 kcal/mol using 2D EXY NMR. Since many of the naturally occurring enamides also have a *cis*-enamide, it was of interest to study in depth the physical properties of *cis*-enamides. The *cis*-*N*-(β-2,6-difluorostyryl)formamide was selected as a model. The NMR studies revealed a rotational barrier for the *cis*-enamide with the same magnitude as the *trans*-enamide. However, the X-ray structure of the *trans*-*trans*-*N*-(β-4-methoxystyryl)formamide (tuberine) showed that the benzene π-plane was coplanar to the π-enamide bond (Figure 5a), while in the *cis*-enamide *N*-(β-2,6-difluorostyryl)formamide (Figure 5b) the styrylamide π-

plane of the double bond was at 48 degrees with respect to the benzene ring π-plane. These structures agree well with computational models. A similar conformational behavior in the molecular modelling study of sanjonine G1 was observed by Zhu *et al.*, where the σ bond in the macrocyle lies out of the plane defined by the aromatic ring.

This subtle difference in the orientation of the double bond in the *trans* and *cis* enamide function and the biological significance prompted us to synthesize and study the biological properties of some model 13-, 14- and 15-membered cyclic enamides and explore the relationship between stereochemistry and biological properties. Our goal in this project was to attempt and introduce the *cis* enamide functionality into a cyclic 13-, 14- and 15-sized lactams, using a *syn*-sulfoxide elimination methodology, and to study these compounds as models for the natural cyclopeptides.

Results and Discussion

Our synthetic strategy for the high membered macrocycles is shown in Scheme 1. It started with the alkylation of an appropriately substituted hydroxybenzaldehyde **1** with allyl bromide under basic conditions. The allyloxybenzaldehydes **2** were subjected to an addition of nitromethane, followed by a subsequent Michael addition of thiophenol to nitrostyrenes **3** to give nitro sulfides **4**. The nitro group was reduced to amino giving compounds **5**, and these were then derivatized with a suitable *n*-alkenyl carboxylic acid to give the amides **6-8** with a diene functionality, which then were ring closed by the RCM method using a Grubbs-Hoveyda first generation catalyst to give the macrocyclic compounds **9-11** in very good yields. The sulfide group was oxidized to sulfoxide and the sulfoxides subjected to thermal elimination to give the *cis*-enamides **12-14** in good yields. This methodology is straightforward compared to the selenocyanate oxidative elimination reported independently by Schmidt and Joullie in the synthesis of the cyclopeptide alkaloids franguline A and nummularine F, respectively.[47] Our initial goal was to find a suitable methodology to construct the required ring system, followed by a syn elimination of the sulfoxide to generate the enamide functional group. Among the various methods known for making cyclopeptides, ethers and esters, catalytic ring-closing olefin metathesis is by far the simplest and most useful tool for making medium-sized ring compounds.[48-56]



Scheme 1. Synthesis of 13, 14 and 15-member lactams via RCM. Reagents and conditions: (a) $CHCl_3$, Br_2; (b) C_3H_5Br, DMF, K_2CO_3; (c) CH_3NO_2, AcOH, $AcONH_4$; (d) PhSH, *N*-Isopropyl-cyclohexylamine, CH_2Cl_2; (e) Zn, HCl, AcOH or SmI_2, MeOH; (f) DCC, DMAP, *n*-alkenyl carboxylic acid or *n*-alkenyl acyl chloride; (g) Grubbs catalyst, DCM; (h) i. $NaIO_4$; ii toluene, K_2CO_3.

Conclusions

We have synthesized 13-, 14- and 15-membered *cis*-enamide macrocycles using Grubbs RCM method in 25, 52 and 46% overall yields, respectively. The *cis*-enamide functional group was successfully introduced into these cyclic lactams by a *syn* sulfoxide elimination. This synthetic methodology provides a simple route to making medium-sized cyclic lactams. These medium-sized cyclic lactams could be used as models to mimic the β-turn in natural proteins, an important marker in understanding their biological activity.[57-60]

Experimental Section

General. All reagents were purchased in the highest quality available and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded using a Varian 500 MHz Spectrometer in $CDCl_3$ with TMS as internal standard and 200 MHz. The chemical shifts are expresed in ppm and the coupling constants (*J*) in Hertz. Electronic impact mass spectra were obtained by direct insertion in Agilent 5975C mass spectrometer. Infrared spectra were recorded on a Spectrum FT-IR 1600 spectrophotometer. Melting points were determined on a Fisher-Johns melting point apparatus and were corrected.

2,4-Dibromo-5-hydroxybenzaldehyde (1b). To a solution of 3-hydroxybenzaldehyde **1a** (40.9 mmol, 5.0 g) in $CHCl_3$ (100 mL) was added bromine (81.7 mmol, 4.2 mL). The resulting solution was stirred at rt for 3 d. The excess bromine was removed with a saturated solution of sodium thiosulfate (20 mL), the organic phase was washed with water and dried over anhydrous Na_2SO_4. Removal of solvent gave a solid which was recrystallized from acetic acid to give **1b** (10.5 g, 85%); mp 134-135 ^{o}C; FTIR (KBr): 3440, 3076, 2877, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.23 (s, 1H), 7.80 (s, 1H), 7.54 (s, 1H), 6.33 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.9, 152.5, 136.5, 133.8, 117.8, 116.8, 116.2; MS(EI) *m/z*: 280 (M^+, 15), 63 (100).

3-Allyloxybenzaldehyde (2a). To a solution of 3-hydroxybenzaldehyde **1a** (81.9 mmol, 10.0 g) and K_2CO_3 (1.5 g) in DMF (100.0 mL) was added allyl bromide (7.8 mL) and the mixture was stirred for 3 h at rt. The reaction mixture was quenched with water (50 mL) and the organic phase was extracted into Et_2O (3×100 mL), dried over Na_2SO_4 and the solvent removed at reduced pressure to give a yellow liquid **2a** (11.0 g, 83%): FTIR (KBr) 3071, 2818, 1697 cm^{-1}; ^{1}H NMR (200 MHz): δ 9.91 (s, 1H), 7.41 (m, 3H), 7.17 (m, 1H), 6.04 (m, 1H), 5.41 (dd, *J* 16.0, 6.0 Hz, 1H), 5.30 (dd, *J* 10.0, 6.0 Hz, 1H), 4.58 (d, *J* 5.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.7, 159.1, 137.7, 132.8, 130.1, 123.6, 122.1, 118.0, 113.1, 68.9; MS(EI) *m/z*: 162 (M^+, 100), 147 (47), 121 (94), 65 (81).

5-Allyloxy-2,4-dibromobenzaldehyde (2b). Compound **2b** was synthesized from compound **1b** (17.85 mmol, 5.0 g) using the same procedure for compound **2a**. A yellow solid **2b** was obtained (5.2 g, 91%); mp 63-64 ^{o}C; IR (KBr) 3082, 2984, 1687 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.23 (s, 1H), 7.83 (s, 1H), 7.37 (s, 1H), 6.10 (m, 1H), 5.49 (dd, *J* 18.0, 4.8 Hz, 1H), 5.34 (dd, *J* 10.0, 4.4 Hz, 1H), 4.65 (dd, *J* 5.0, 1.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.8, 154.5, 137.5, 132.9, 131.5, 120.4, 118.5, 117.8, 112.2, 69.9; MS(EI) *m/z*: 320 (M^+, 100), 279 (48), 239 (27), 223 (50).

(*E*)-1-(Allyloxy)-3-(2-nitrovinyl)benzene (3a). To a solution of **2a** (12.3 mmol, 2.0 g) in glacial AcOH (20 mL) was added NH_4OAc (0.4 g) and nitromethane (2.0 mL). The solution was heated at reflux with magnetic stirring for 1 h. The mixture was cooled to rt, the resulting dark yellowish precipitate was collected by filtration and was washed with water. The solid was dissolved in CH_2Cl_2 (40.0 mL), filtered through a plug of silica and then the organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a yellowish solid (1.8 g, 70%); mp 59-60 ^{o}C; FTIR (KBr): 3112, 3033, 2900, 1628, 1595 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96 (d, *J* 13.6 Hz, 1H), 7.55 (d, *J* 13.6 Hz, 1H), 7.36 (dd, *J* 9.0, 7.6 Hz, 1H), (m , 4H), 7.26 (td, *J* 7.7, 1.1 Hz, 1H), 7.00 (m, 2H), 6.06 (m, 1H), 5.43 (dd, *J* 17.3, 3.2 Hz, 1H), 5.32 (dd, *J* 10.4, 1.4 Hz, 1H), 4.58 (td, *J* 5.6, 1.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.8, 138.8, 137.1, 132.1, 131.1, 130.2, 121.7, 118.5, 118.0, 114.7, 68.9; MS(EI) *m/z*: 205 (M^+, 100), 159 (64), 89 (68), 63 (63).

(*E*)-1-(allyloxy)-2,4-dibromo-5-(2-nitrovinyl)benzene (3b). Compound **3b** was synthesized from compound **2b** (9.4 mmol, 3.0 g) using the same procedure as for compound **2a**. A yellow solid was obtained (3.4 g, 70%); mp 109-110 ^{o}C; FTIR (KBr): 3103, 2937, 1629, 1577 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.28 (d, *J* 13.6 Hz, 1H), 7.86 (s, 1H), 7.50 (d, *J* 13.6 Hz, 1H), 6.99 (s, 1H), 6.05 (m, 1H), 5.49 (dd, *J* 17.6, 1.8 Hz, 1H), 5.38 (dd, *J* 10.3, 1.4 Hz,

1H), 4.66 (t, *J* 1.4 Hz, 1H), 4.64 (t, *J* 1.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.7, 138.6, 137.8, 136.8, 131.3, 129.6, 118.4, 117.3, 117.0, 111.6, 70.1; MS(EI) *m/z*: 363 (M^+, 75), 317(45), 215 (93), 62 (100).

1-Allyloxy-3-(2-nitro-1-phenylsulfanylethyl)benzene (4a). Compound **3a** (32.2 mmol, 6.6 g) was dissolved in CH_2Cl_2 (30.0 mL) and to the solution was added thiophenol (44.3 mmol, 4.5 mL) and 4 drops of *N*-isopropylcyclohexylamine. The resulting solution was stirred for 1 h at rt. The solution was concentrated and the crude reaction mixture was poured onto silica gel, and then was subjected to flash chromatography using CH_2Cl_2:hexane (20:80) as eluting solvent. Removal of the solvent gave a dark yellow oil (9.3 g, 92%); FTIR (ATR) 3059, 2916, 1554 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33 (m, 5H), 7.20 (m, 1H), 6.81 (m, 3H), 6.03 (m, 1H), 5.38 (dt, *J* 17.0, 1.8 Hz, 1H), 5.27 (dt, *J* 8.0, 1.6 Hz, 1H), 4.79 (m, 3H), 4.64 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.8, 137.8, 133.7, 133.0, 131.9, 130.0, 129.4, 128.8, 120.0, 117.9, 114.9, 114.2, 78.6, 69.0, 50.0; MS(EI) *m/z*: 315 (M^+, 100), 269 (26), 160 (96), 135 (70).

1-Allyloxy-2,4-dibromo-5-(2-nitro-1-phenylsulfanylethyl)benzene (4b). Compound **4b** was synthesized from compound **3b** (4.3 mmol, 1.6 g) using the same procedure for compound **4a**. A thick yellow liquid was obtained (1.8 g, 90%); FTIR (ATR): 3294, 3076, 2023, 1648, 1552 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.26 (m, 5H), 6.84 (s, 1H), 5.96 (m, 1H), 5.42 (dd, *J* 16.0, 2.0 Hz, 1H), 5.34 (m, 2H), 4.70 (m, 2H), 4.45 (dt, *J* 4.0, 1.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.2, 136.8, 135.0, 133.9, 131.6, 130.7, 129.2, 128.9, 118.2, 114.8, 113.1, 112.4, 77.2, 69.9, 48.5; MS(EI) *m/z*: 473 (M^+, 32), 426 (6), 348 (17), 318 (100).

2-(3-Allyloxyphenyl)-2-phensulfanylethanamine (5a). A stirred mixture of **4a** (31.7 mmol, 10.0 g), zinc (316 mmol, 20.6 g) and AcOH (80 mL), was cooled in an ice/water bath, and concentrated HCl (67 mL) added dropwise and then stirred overnight at rt. The highly acidic solution was then treated with NH_4OH (2 N) until the pH was about 10. The oily precipitate formed was extracted with CH_2Cl_2 (2×100 mL), the extact dried with Na_2SO_4 and concentrated to give the amine as a yellow oil (3.6 g, 40%). The crude amine was then used in the next step without further purification. FTIR (ATR): 3367, 3064, 2917, 1582, 1479 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34 (m, 5H), 6.83 (m, 4H), 6.10 (m, 1H), 5.36 (d, *J* 18.0 Hz, 1H), 5.24 (d, *J* 10.0 Hz, 1H), 4.47 (m, 2H), 4.10 (t, *J* 7.0 Hz, 1H), 3.08 (d, *J* 7.0 Hz, 1H), 2.01 (brs, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.7, 141.7, 134.0, 133.2, 132.3, 129.6, 128.8, 127.2, 120.6, 117.8, 114.5, 113.8, 68.9, 56.5, 46.5; MS(EI) *m/z*: 285 (M^+, 5), 256 (100), 215 (30), 185 (14).

2-(3-Allyloxy-4,6-dibromophenyl)-2-phensulfanylethanamine (5b). To a solution of compound **4b** (0.5 g, 1.0 mmol) in dry MeOH (1.0 mL) was added a 0.1 M solution of SmI_2 (100 mL, 10.0 mmol) in THF under Ar atmosphere at rt. The mixture was stirred for 24 h at the same temperature. After this time, it was added dropwise to an aqueous solution of NaOH until the blue colored suspension turned colorless. The resulting suspension was then extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent was evaporated to afford the crude amine as a clear yellow liquid (0.4 g, 75%); IR (ATR): 3380, 3064, 2917, 1643, 1578 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.22 (m, 5H), 6.96 (s, 1H), 5.98 (m, 1H), 5.42 (d, *J* 16.0 Hz, 1H), 5.28 (d, *J* 10.0 Hz, 1H), 4.67 (t, *J* 7.0 Hz, 1H), 4.51(m, 2H), 3.05 (d, *J* 7.0 Hz, 2H), 2.47 (brs, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.4, 139.3, 136.2, 133.4, 131.9, 131.8, 128.9, 127.4, 118.2, 115.2, 113.5, 111.7, 69.8, 54.9, 46.5; MS(EI) *m/z*: 443 (M^+, 20), 414 (100), 363 (31).

***N*-(2-(3-Allyloxyphenyl)-2-(phenylthio)ethyl)pent-4-enamide (6a).** To an ice cooled solution of amine **5a** (1.3 mmol, 0.4 g) in CH_2Cl_2 (30 mL) was added catalytic amounts of DMAP and 4-pentenoyl chloride (1.4 mmol, 0.2 mL). The solution was stirred overnight and filtered through a silica plug. Then the solution was concentrated and the residue was purified by circular chromatography using CH_2Cl_2:MeOH (97:3) as eluting solvent. Removal of the solvent gave a yellow oil (0.4 g, 75%); FTIR (ATR): 3064, 2917, 1643, 1539 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.22 (m, 4H), 6.82 (m, 3H), 6.00 (m, 1H), 5.73 (m, 2H), 5.39 (d, *J* 17.4 Hz, 1H), 5.27 (d, *J* 10.9 Hz, 1H), 4.98 (d, *J* 15.0 Hz, 1H), 4.94 (d, *J* 10.0 Hz, 1H), 4.48 (m, 2H), 4.33 (t, *J* 7.4 Hz, 1H), 3.75 (m,

1H), 3.60 (m, 1H), 2.29 (m, 2H), 2.16 (t, *J* 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 159.0, 141.1, 137.1, 134.1, 133.3, 132.1, 129.9, 129.1, 127.5, 120.6, 117.9, 115.7, 114.5, 114.3, 68.9, 52.3, 44.4, 35.8, 29.6; MS(EI) *m/z*: 367 (M^+, 10), 268 (100), 258 (66), 176 (78). HRMS(FAB) calcd for $C_{22}H_{25}NO_2S$ $(M+H)^+$ 368.1684. Found 368.1699.

***N*-(2-(5-allyloxy-2,4-dibromophenyl)-2-(phenylthio)ethyl)pent-4-enamide (6b).** Compound **6b** was synthesized from **5b** (1.5 mmol, 0.7 g), using the same procedure as for compound **6a**. A dark yellow liquid was obtained (0.4 g, 57%); FTIR (neat) 3289, 3073, 2928, 1647, 1545, 1467, 1245 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.26 (m, 5H), 6.34 (s, 1H), 5.99 (m, 1H); 5.20 (m, 2H), 5.47 (dd, *J* 16.0, 4.0 Hz, 1H), 5.30 (dd, *J* 9.0, 4.0 Hz, 1H), 5.03 (dd, *J* 15.0, 4.0 Hz, 1H), 4.95 (m, 1H), 4.78 (t, *J* 7.0, Hz, 1H), 4.49 (m, 2H), 2.70 (m, 2H), 2.38 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 154.2, 138.1, 136.4, 136.1, 132.3, 132.2, 131.7, 128.8, 127.6, 117.9, 115.4, 115.0, 113.1, 111.8, 69.7, 50.7, 42.9, 35.6, 29.3; MS(EI) *m/z*: 525 (M^+, 12), 446 (85), 416 (100), 334 (78).

***N*-(2-(3-allyloxyphenyl)-2-(phenylthio)ethyl)hex-5-enamide 7a.** To a well stirred and ice cooled solution of DCC (7.7 mmol, 1.6 g), under argon, DMAP (0.05 g) and 5-hexenoic acid (7.7 mmol, 0.9 mL) in dry THF (100 mL) was added the amine **5a** (7.7 mmol, 2.2 g). The mixture was strirred at rt for 24 h then it was filtered, dried with Na_2SO_4 and concentrated. The residue was purified using circular chromatography eluting with CH_2Cl_2/MeOH (97:3) to afford the product as a yellow liquid (2.4 g, 80%); FTIR (neat): 3293, 3073, 2926, 1644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 2H), 7.21 (m, 4H), 6.83 (m, 3H), 6.03 (m, 1H), 5.71 (m, 2H), 5.39 (d, *J* 16.0 Hz, 1H), 5.27 (d, *J* 11.0 Hz, 1H), 4.95 (m, 2H), 4.48 (m, 2H), 4.34 (t, *J* 8.0 Hz, 1H), 3.75 (m, 1H), 3.61 (m,1H), 2.06 (m, 2H), 2.00 (m, 2H), 1.65 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8, 158.8, 140.9, 137.8, 134.0, 133.1, 131.9, 129.7, 128.9, 127.3, 120.4, 117.7, 115.3, 114.3, 114.1, 68.8, 52.2, 44.2, 35.7, 33.0, 24.6; MS(EI) *m/z*: 381 (M^+, 12), 268 (100), 255 (55), 176 (78); HRMS(FAB) Calcd for $C_{23}H_{27}N_2OS$ $(M+H)^+$ 382.18407. Found 382.18410.

***N*-(2-(3-allyloxyphenyl)-2-(phenylthio)ethyl)hept-6-enamide 8a.** Compound **8a** was synthesized from the amine **5a** (7.0 mmol, 2.0 g) using the procedure for **7a** and 0.95 mL of 6-heptenoic acid (7.0 mmol, 0.9 g). A dark yellow liquid was obtained (2.3 g, 82%); FTIR (neat): 3295, 3064, 2927, 1644 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (m, 2H), 7.22 (m, 4H), 6.82 (m, 3H), 6.03 (m, 1H), 5.75 (m, 1H), 5.59 (s, 1H), 5.39 (dd, *J* 17.0 , 2.0 Hz, 1H), 5.27 (dd, *J* 10.0, 2.0 Hz, 1H), 4.97 (dd, *J* 17.0, 2.0 Hz, 1H), 4.92 (dd, *J* 11.0 , 2.0 Hz, 1H), 4.49 (m, 2H), 4.34 (t, *J* 8.0 Hz, 1H), 3.77 (m, 1H), 3.61 (m, 1H), 2.07 (t, *J* 7.0 Hz, 2H), 2.02 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.9, 158.9, 140.9, 138.4, 134.0, 133.1, 131.9, 129.7, 128.9, 127.3, 120.4, 117.7, 114.7, 114.3, 114.2, 68.8, 52.2, 44.2, 36.5, 33.4, 28.4, 25.0; MS(EI) *m/z*: 395 (M^+, 13), 286 (50), 268 (100), 176 (80).

[2-(5-allyloxy-2,4-dibromophenyl)-2-(phenylsulfanyl)ethyl]-6-heptenamide (8b). Compound **8b** was synthesized from **5b** (1.5 mmol, 0.7 g), using the procedure for compound **7a**. A dark yellow liquid was obtained (0.4 g, 57%); FTIR (neat): 3291, 3077, 2929, 1649 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.30 (m, 5H), 6.86 (s, 1H), 6.00 (m, 1H), 5.75 (m, 1H), 5.55 (s, 1H), 5.45 (dd, *J* 17.0 , 2.0 Hz, 1H), 5.30 (dd, *J* 10.0, 2.0 Hz, 1H), 4.97 (dd, *J* =17.0, 2.0 Hz, 1H), 4.93 (dd, *J* 10.0, 2.0 Hz, 1H), 4.78 (t, *J* 8.0 Hz, 1H), 4.49 (m, 2H), 3.76 (m, 1H), 3.65 (m, 1H), 2.08 (m, 2H), 2.01 (m, 2H), 1.55 (m, 4H), 1.32 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8, 154.6, 138.5, 138.4, 136.4, 132.7, 132.6, 132.1, 129.05, 127.9, 118.2, 115.3, 114.7, 113.5, 112.2, 69.9, 50.8, 43.1, 36.5, 33.5, 28.4, 24.9. MS(EI) *m/z*: 554 (M^+, 6), 474 (42), 444 (100), 426 (60); HRMS(FAB) calcd for $C_{24}H_{28}Br_2NO_2S$ $(M+H)^+$ 552.02075. Found 552.02080.

11-phenylsulfanyl-2-oxa-9-azabicyclo[10.3.1]hexadeca-1(16),4*E*,12,14-tetraen-8-one (9a). To solution of diene **6a** (80.0 mg, 0.2 mmol) in 55 mL of dry CH_2Cl_2 (0.004 M) was added the Hoveyda-Grubbs catalyst (9.0 mg, 0.014 mmol) and refluxed for 12 h. The reaction was carried out in an open system and to remove

ethylene from the system a very gentle flow of argon was used. Then, the reaction mixture was filtered through a short fluorisil pad to remove the catalyst residues. The solvent was evaporated under reduced pressure and the crude product was purified using circular chromatography to give the macrocycle product (53.4 mg, 73% yield). Mp 146-148 ^{o}C; FTIR (KBr): 3292, 3062, 2922, 1655, 1635, 1534 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.41 (dt, *J* 6.5, 1.4 Hz, 2H), 7.24 (m, 4H), 6.94 (dt, *J* 7.5, 1.0 Hz, 1H), 6.82 (dd, *J* 8.1, 1.8 Hz, 1H), 6.76 (t, *J* 1.9 Hz, 1H), 5.62 (m, 1H); 5.51 (dt, *J* 16.0, 5.0 Hz, 1H), 5.45 (brs, 1H), 4.64 (m, 2H), 4.50 (dd, *J* 8.7, 4.1 Hz, 1H), 4.05 (m, 1H), 3.14 (m, 1H), 2.48 (m, 1H), 2.35 (m, 1H), 2.27 (m, 1H), 2.04 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.8, 157.1, 139.6, 134.1, 133.9, 131.5, 130.0, 129.1, 127.8, 127.3, 119.6, 117.9, 116.9, 69.1, 51.0, 44.9, 37.2, 27.7; MS(EI) *m/z*: 339 (M^+, 33), 230 (100), 136 (45); HRMS(FAB) calcd for $C_{20}H_{22}NO_2S$ $(M+H)^+$ 340.13712. Found 340.13716.

13,15-Dibromo-11-phenylsulfanyl-2-oxa-9-azabicyclo[10.3.1]hexadeca-(16),4*E*,12,14-tetraen-8-one (9b). Compound **9b** was synthesized using the same procedure for compound **9a** using diene **6b** (55.2 mg, 0.1 mmol). A gray solid was obtained (37.4 mg, 72%); FTIR (KBr): 3281, 3064, 2926, 1648, 1544 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.40 (m, 2H), 7.29 (m, 3H), 6.72 (s, 1H), 5.69 (m, 1H), 5.71 (dt, *J* 16.0, 5.0 Hz, 1H), 5.43 (brs, 1H), 4.49 (t, *J* 8.0, 1H), 4.65 (m, 2H), 4.02 (m, 1H), 4.52 (m, 1H), 2.03 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 156.2, 142.1, 136.4, 135.2, 130.1, 129.9 128.1 128.0 127.2, 117.2, 116.2, 112.8, 70.2, 50.80, 45.2, 38.3, 38.1; MS(EI) *m/z*: 497 (M^+, 55), 388 (100), 355 (12).

12-Phenylsulfanyl-2-oxa-10-azabicyclo[11.3.1]heptadeca-1(17),4*E*,13,15-tetraen-9-one (10a). Compound **10a** was synthesized using the same procedure as for compound **9a** using diene **7a** (2.6 mmol, 1.0 g). A gray solid was obtained (0.5 g, 52%); mp 158-160 ^{o}C; FTIR (KBr): 3298, 3056, 2928, 1648, 1595 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.25 (m, 4H), 7.04 (d, *J* 7.6 Hz, 1H), 6.80 (dd, *J* 8.2, 2.4 Hz, 1H), 6.64 (t, *J* 1.7 Hz, 1H), 5.70 (m, 1H), 5.46 (m, 1H), 5.32 (brs, 1H), 4.69 (dd, *J* 10.2, 4.3 Hz, 1H), 4.62 (m, 2H), 4.00 (m, 1H), 3.10 (m, 1H), 2.29 (m, 2H), 2.10 (m, 1H), 1.96 (m, 1H), 1.84 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 157.6, 140.0, 134.4, 134.3, 131.1, 130.0, 129.1, 127.8, 127.0, 119.2, 117.1, 113.8, 67.8, 49.8, 45.5, 34.4, 33.9, 20.9; MS(EI) *m/z*: 353 (M^+, 50), 244 (100), 228 (32); HRMS(FAB) calcd for $C_{21}H_{24}NO_2S$ $(M+H)^+$ 354.15277. Found 354.15290.

(*E*)-13-(phenylthio)-2-oxa-11-aza-1(1,3)-benzenacyclotridecaphan-4-en-10-one (11a). Compound **11a** was synthesized using the same procedure as for compound **9a** using diene **8a** (308 mg, 0.78 mmol) to give brown crystals (204 mg, 71 % yield); mp 118-121 °C; FTIR (KBr) 3287, 3056, 2930, 1646, 1594 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (m, 2H), 7.27 (m, 4H), 7.21 (t, *J* 7.8 Hz, 1H), 6.96 (d, *J* 8.0 Hz, 1H), 6.87 (dd, *J* 8.0, 4.0 Hz, 1H), 6.70 (t, *J* 1.8 Hz, 1H), 5.63 (m, 1H), 5.47 (m, 1H), 5.23 (brs, 1H), 4.65 (m, 1H), 4.60 (m, 1H) 4.29 (dd, *J* 10.0, 4.0 Hz, 1H), 4.16 (m, 1H), 3.24 (m, 1H), 2.30 (m, 1H), 2.0 (m, 2H), 1.44 (m, 2H), 1.30 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.3, 158.2, 140.2, 134.6, 134.3, 131.4, 130.4, 129.0, 127.1, 126.7, 119.1, 117.6, 115.7, 68.6, 50.9, 44.3, 36.6, 31.5, 27.6, 25.6; EM(IE) *m/z*: 367 (M^+, 10), 258 (100), 228 (37). HRMS(FAB) calcd for $C_{22}H_{26}NO_2S$ $(M+H)^+$ 368.16842. Found 368.16847.

15,17-Dibromo-13-phenylsulfanyl-2-oxa-11-azabicyclo[12.3.1]octadeca-1-(18),4,14,16-tetraen-10-one (11b). To solution of diene **8b** (118.4 mg, 0.214 mmol) in 215 mL of dry CH_2Cl_2 (0.001 M) was added the Hoveyda-Grubb´s catalyst (6.7 mg, 0.011 mmol) and the mioxture heated at reflux for 12 h. The reaction was carried out in an open system and to remove ethylene from the system a very gentle flow of Ar was used. Then, the reaction mixture was filtered through a short fluorisil pad to remove the catalyst residues. The solvent was evaporated under reduced pressure and the crude product was purified using circular chromatography to give the macrocyclic product (113 mg, 80% yield). FTIR (ATR): 3292, 3059, 2930, 2859, 1651, 1551 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.43 (m, 2H), 7.31 (s, 3H), 6.64 (s, 1H), 5.70 (m, 1H), 5.73 (dt, *J* 16.0, 5.0 Hz, 1H), 5.67 (brs, 1H), 4.80 (t, *J* 8.0 Hz, 1H), 4.67 (m, 2H), 4.20 (m, 1H), 3.4 (m, 1H), 2.02 (m, 4H), 1.40 (m, 2H),

1.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 138.3, 137.2, 137.0, 135.4, 133.2, 131.9, 131.3, 129.2, 129.1, 127.6, 127.4, 126.5, 125.9, 70.2, 51.2, 40.9, 36.2, 31.2, 26.5, 24.7, 19.9; MS(EI) *m/z*: 525 (M^+, 60), 414 (100), 381 (12); MS(ESI) *m/z*: 526 $(M+H)^+$; HRMS(FAB) calcd for $C_{22}H_{24}Br_2NO_2S$ $(M+H)^+$ 523.98945. Found 523.98990.

2-Oxa-9-azabicyclo[10.3.1]hexadeca-1(16),4*E*,11*Z*(10),12,14-penten-8-one (12a). To a solution of sulfide **9a** (70 mg, 0.21 mmol) in MeOH (5.0 mL) were added dropwise 5.0 mL of an aqueous solution of sodium periodate (88.3 mg, 0.42 mmol) at rt and the mixture stirred for 2 h. The mixture was extracted with CH_2Cl_2 (3×5 mL) and the combined organic phase was dried with Na_2SO_4, filtered and the solvent was evaporated to give the sulfoxide as a colorless oil. To a solution of sulfoxide in toluene (20 mL) was added K_2CO_3 (189 mg, 1.4 mmol) and stirred at reflux for 3 h. The solvent was evaporated and the residue was dissolved with CH_2Cl_2 (20 mL) and washed with brine. The organic phase was dried with Na_2SO_4, filtered and the solvent was evaporated to give a crude product that was purified by circular chromatography to give a colorless oil (44.6 mg, 94% yield); FTIR (KBr) 3292, 3062, 2922, 1655, 1635, 1534 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.91 (d, *J* 10.0 Hz, 1H), 7.24 (m, 1H), 6.96 (dd, *J* 11.0, 9.0 Hz, 1H), 6.84 (m, 2H), 6.74 (d, *J* 8.0 Hz, 1H), 5.87 (m, 1H), 5.83 (d, *J* 10.0 Hz, 1H); 5.67 (dt, *J* 16.0 , 5.0 Hz, 1H), 4.78 (dd, *J* 5.0, 1.0 Hz, 2H), 2.5 (m, 2H), 2.47 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.6, 157.2, 135.7, 134.0, 130.9, 130.2, 122.7, 120.8, 116.9, 114.9, 111.1, 69.4, 35.9, 26.9; MS(EI) *m/z*: 229 (M^+, 50), 216 (35), 159 (100); HRMS(FAB) calcd for $C_{14}H_{15}NO_2$ $(M+H)^+$ 230.1103. Found 230.1099.

13,15-Dibromo-2-oxa-9-azabicyclo[10.3.1]hexadeca-1(16),4*E*,11*Z*(10),12,14-penten-8-one (12b). Compound **12b** was synthesized from compound **9b** (37.4 mg, 0.075 mmol) using the same procedure for compound **12a**. Colorless oil was obtained (29.0 mg, 99.7%); FTIR (KBr) 3280, 3050, 2926, 1648, 1544 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (brs, 1H), 7.80 (s, 1H), 7.30 (dd, *J* 10.0, 9.0 Hz, 1H), 6.50 (s, 1H), 6.18 (d, *J* 10.0 Hz, 1H), 5.70 (m, 1H), 5.60 (dt, *J* 16.0, 5.0 Hz, 1H), 4.61 (d, *J* 5.0 Hz, 2H), 2.22 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 156.2, 136.4, 135.2, 129.3 128.5, 124.5, 121.2, 113.2, 112.8, 106.7, 70.2, 38.3, 38.1; MS(EI) *m/z*: 387 (M^+, 58). 307 (43), 253 (100); HRMS(FAB) calcd for $C_{14}H_{13}Br_2NO_2$ $(M+H)^+$ 385.9313. Found 385.9309.

2-Oxa-10-azabicyclo[11.3.1]heptadeca-1(17),4*E*,12*Z*(11),13,15-penten-9-one (13a). Compound **13a** was synthesized from compound **10a** (17.0 mg, 0.05 mmol) using the same procedure as for compound **12a**. A colorless oil was obtained (11.0 mg, 94%); FTIR (KBr): 3281, 3056, 2926, 1650, 1596 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.50 (brs, 1H), 7.24 (t, *J* 8.0 Hz, 1H), 6.88 (brs, 1H), 6.86 (dd, *J* 11.0, 9.0 Hz, 1H), 6.81 (m, 1H), 6.73 (d, *J* 8.0 Hz, 1H), 5.88 (d, *J* 10.0 Hz, 1H), 5.81 (dt, *J* 16.0, 5.0 Hz, 1H), 5.68 (m, 1H), 4.68 (dd, *J* 6.0, 1.0 Hz, 2H), 2.27 (m, 4H), 1.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 158.2, 136.7, 134.0, 130.3, 129.4, 122.8, 120.5, 116.6, 112.0, 111.7, 68.3, 36.5, 34.4, 24.3; MS(EI) *m/z*: 243 (M^+, 50), 135 (100); HRMS(FAB) calcd for $C_{15}H_{17}NO_2$ $(M+H)^+$ 244.1259. Found 244.1255.

2-Oxa-11-aza-bicyclo[12.3.1]octadeca-1(18),4*E*,13*Z*(12),14,16-penten-10-one (14a). Compound **14a** was synthesized from compound **11a** (204 mg, 0.6 mmol) using the same procedure as for compound **12a**. A colorless oil was obtained (86.3 mg, 60%); FTIR (ATR): 3287, 3056, 2930, 1646, 1594 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (brs, 1H), 7.24 (t, *J* 8.0 Hz, 1H), 6.95 (dd, *J* 11.0, 9.0 Hz, 1H), 6.83 (brs, 2H), 6.72 (dd, *J* 8.0, 4.0 Hz, 1H), 5.90 (d, *J* 10.0 Hz, 1H), 5.83 (m, 1H), 5.69 (m, 1H), 4.79 (d, *J* 5.0 Hz, 2H), 2.03 (m, 4H), 1.43 (m, 2H), 1.3 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.3, 158.2, 136.0, 132.3, 129.0, 128.9, 120.7, 119.1, 113.6, 113.0, 110.4, 75.7, 39.3, 28.7, 27.6, 25.6; MS(EI) *m/z*: 257 (M^+, 100), 228 (25), 215 (16). HRMS(FAB) calcd for $C_{16}H_{19}NO_2$ $(M+H)^+$ 258.1416. Found 258.1421.

15,17-Dibromo-2-oxa-11-azabicyclo[12.3.1]octadeca-1(18),4*E*,13*Z*(12),14,16-penten-10-one 14b. Compound **14b** was synthesized from compound **11b** (113 mg, 0.2 mmol) using the same procedure as for compound **12a**. A colorless oil was obtained (41.1 mg, 45%); FTIR (KBr): 3285, 3066, 2930, 1650, 1594 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 (brs, 1H), 7.80 (s, 1H), 7.02 (dd, *J* 11.0, 9.0 Hz, 1H), 6.55 (s, 1H), 6.10 (d, *J* 10.0 Hz, 1H), 5.61 (m, 2H), 4.61 (d, *J* 5.0 Hz, 2H), 2.16 (m, 2H), 2.20 (m, 2H), 1.55 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 156.3,

136.1, 135.9, 132.2, 128.7, 124.1, 119.4, 113.5, 112.0, 110.7, 70.1, 40.9, 28.5, 26.5, 21.1; MS(EI) *m/z*: 415 (M^+, 45), 317 (100), 238 (70); HRMS(FAB) calcd for $C_{16}H_{17}Br_2NO_2$ $(M+H)^+$ 413.9626. Found 413.9623.

Acknowledgements

We gratefully acknowledge support for this project by COSNET grant 421.03-P (2003) and CONACYT (F264-E9207).

References

1. Tschesche, R.; Kaussmann, E. U. The Alkaloids: Manske, R. H. F., Ed.; Academic Press: New York; 1975; pp 164-205. http://dx.doi.org/10.1016/S1876-0813(08)60276-6
2. Schmidt, U.; Liberknecht, A.; Haslinger, E. The Alkaloids: Brossi, A., Ed.; Academic Press: New York 1985; pp 299-326. http://dx.doi.org/10.1016/S0099-9598(08)60197-2
3. Tan, N-H.; Zhou, J. *Chem. Rev.* **2006**, *106*, 840. http://dx.doi.org/10.1021/cr040699h
4. Joullie, M. M.; Richard, D. J. *Chem. Commun.* **2004**, 2011. http://dx.doi.org/10.1039/B400334A
5. Han, J.; Ji, C. J.; He, W.-J.; Shen, Y.; Leng, Y.; Xu, W.-Y.; Fan, G.-Z.; Kong, L.-D.; Tan, N.-H. *J. Nat. Prod.* **2011**, *74*, 2571. http://dx.doi.org/10.1021/np200755t
6. Kaleen, W. A.; Nisar, M.; Qayum, M.; Zia-Ul-Haq, M.; Adhikari, A.; De Feo, V. *J. Mol. Sci.* **2012**, *13*, 11520. http://dx.doi.org/10.3390/ijms130911520
7. Schmidt, U.; Lieberknecht, A.; Bökens, H.; Griesser, H. *Angew. Chem. Int. Ed.* **1981**, *20*, 1026. http://dx.doi.org/10.1002/anie.198110261
8. Laïb, T.; Zhu, J. *Tetrahedron Lett.* **1998**, *39*, 283. http://dx.doi.org/10.1016/S0040-4039(97)10513-5
9. Lagarias, J. C.; Houghten, R. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 8202. http://dx.doi.org/10.1021/ja00494a030
10. Gournelis, D. C.; Laskaris, G. G.; Verpoorte, R. *Nat. Prod. Rep.* **1997**, 75. http://dx.doi.org/10.1039/NP9971400075
11. Zhao, S.; Juang, B.; Peng, W.; He, W.; Xu, H.; Ji, C.; Han, J.; Zhen, Y.; Song, W.; Tan, N. *Chin. J. Chem.* **2012**, *30*, 1213. http://dx.doi.org/10.1002/cjoc.201200508
12. Goyal, M.; Prakash, B.; Sasmal, D. *Spatula DD* **2012**, 2, 107. http://dx.doi.org/10.5455/spatula.20120422080614
13. Zhao, S.; Kuang, B.; Peng, W.; He, W.; Xu, H.; Ji, C.; Han, J.; Zhen, Y.; Song, W.; Tan, N. *Chin. J. Chem.* **2012**, *30*, 1213. http://dx.doi.org/10.1002/cjoc.201200508

14. Aguirre, G.; Somanathan, R.; Hellberg, L. H. *J. Fluorine Chem.* **1998**, *90*, 5. http://dx.doi.org/10.1016/S0022-1139(98)00143-2
15. Somanathan, R.; Rivero, I. A.; Aguirre, G.; Ramirez, M.; Hellberg, L. H.; Bakir, F. *Synth. Commun.* **1996**, *26*, 1023. http://dx.doi.org/10.1080/00397919608003707
16. Obrecht, J.; Hellberg, L. H.; Somanathan, R. *Chem. Commun.* **1987**, 1219. http://dx.doi.org/10.1039/C39870001219
17. Osuna-Ramírez, M.; Aguirre, G.; Somanathan, R.; Molins, E. *Tetrahedron: Asymmetry* **2002**, *13*, 2261. http://dx.doi.org/10.1016/S0957-4166(02)00586-4
18. Osuna-Ramírez, M.; Narvaez-Garayzar, O. F.; Somanathan, R.; Aguirre, G. *J. Mex. Chem. Soc.* **2011**, *55*, 57.
19. Kirkuk, P.; Moore, R. *Tetrahedron Lett.* **1983**, *24*, 2087. http://dx.doi.org/10.1016/S0040-4039(00)81851-1
20. Anderson, R. J. *Tetrahedron Lett.* **1978**, *19*, 2541. http://dx.doi.org/10.1016/S0040-4039(01)94821-X
21. Anderson, R. J.; Stonard, R. J. *Can. J. Chem.* **1979**,*57*, 2325. http://dx.doi.org/10.1139/v79-372
22. Bruening, R. C.; Oltz, E. M.; Furakawa, J.; Nakanishi, K.; Kustin, K. *J. Nat. Prod.* **1986**, *49*, 193. http://dx.doi.org/10.1021/np50044a001
23. Oltz, E. M.; Bruening, R. C.; Smith, M. J.; Kustin, K.; Nakanishi, K. *J. Am. Chem. Soc.* **1988**, *110*, 6162. http://dx.doi.org/10.1021/ja00226a035
24. Azumi, K.; Yokisawa, H.; Ishii, S. *Biochemistry* **1990**, *29*, 159. http://dx.doi.org/10.1021/bi00453a021
25. Ohkuma, K.; Anzai, K.; Suzuki, S. *J. Antibiot.* **1962**, *15*, 115.
26. Umezawa, H.; Imoto, M.; Sawa, T.; Isshiki, K.; Matsuda, M.; Uchidda, T.; Linuma, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1986**, *39*, 170. http://dx.doi.org/10.7164/antibiotics.39.170
27. Kagamizono, T.; Sakai, N.; Arai, K.; Kobinata, K.; Osada, H. *Tetrahedon Lett.* **1997**, *38*, 1223. http://dx.doi.org/10.1016/S0040-4039(97)00022-1
28. Chatterjee, A.; Chakrabarty, M.; Kundu, A. B. *Austr. J. Chem.* **1975**, *28*, 457. http://dx.doi.org/10.1071/CH9750457
29. Govidachari, T.; Premila, M. *Phytochemistry* **1983**, *22*, 755. http://dx.doi.org/10.1016/S0031-9422(00)86977-0
30. Burke, B. A.; Philip, S. *Heterocycles* **1985**, *23*, 257. http://dx.doi.org/10.3987/R-1985-02-0257
31. Burke, B. A.; Perkins, H. *Tetrahedron Lett.* **1978**, *19*, 2723. http://dx.doi.org/10.1016/S0040-4039(01)91587-4
32. Galanis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H.; Boyd, M. R. *J. Org. Chem*. **1997**, *62*, 8968. http://dx.doi.org/10.1021/jo9716237
33. Kim, J. W.; Shin-Ya, K.; Furihata, K.; Hyakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153-155. http://dx.doi.org/10.1021/jo9814997
34. Erickson, K. L.; Beutler, J. A.; Cardellina II, J. H.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188. http://dx.doi.org/10.1021/jo971556g
35. Erickson, K. L.; Beutler, J. A.; Cardellina II, J. H.; Boyd, M. R. *J. Org. Chem.* **2001**, 66, 1532. http://dx.doi.org/10.1021/jo004040x

36. Jensen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913. http://dx.doi.org/10.1002/(SICI)1099-0690(200003)2000:6<913::AID-EJOC913>3.0.CO;2-L
37. McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina II, J. H.; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805. http://dx.doi.org/10.1021/jo980939r
38. Suzumura, K.-I.; Takahashi, I.; Matsumoto, H.; Nagai, K.; Setiawan, B.; Rantiatmodjo, R. M.; Suzuki, K.-I.; Nagano, N. *Tetrahedron Lett.* **1997**, *38*, 7573. http://dx.doi.org/10.1016/S0040-4039(97)01785-1
39. Xie, X.-S.; Padron, D.; Liao, X.; Wang, J.; Roth, M. G.; de Brabander, J. K. *J. Biol. Chem.* **2004**, *279*, 19755. http://dx.doi.org/10.1074/jbc.M313796200
40. Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 4308. http://dx.doi.org/10.1002/1521-3773(20001201)39:23<4308::AID-ANIE4308>3.0.CO;2-4
41. Wu, Y.; Seguil, O. R.; De Brabander, J. K. *Org. Lett.* **2000**, *2*, 4241. http://dx.doi.org/10.1021/ol0068086
42. Wu, Y.; Liao, X.; Wang, R.; Xie, X.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245. http://dx.doi.org/10.1021/ja0177713
43. Shih, C. ; Teicher, B. A. *Current Pharm. Design* **2001**, *7*, 1259. https://doi.org/10.2174/1381612013397474
44. Stachel, S. J.; Chapell, M. D.; Lee, C. B.; Danishefsky, S. J.; Chou, T.-C.; He, L.; Horwitz, S. B. *Org. Lett.* **2000**, *2*, 1637. http://dx.doi.org/10.1021/ol005932m
45. Dimopoulos, M. A.; Mitsiades, C. S.; Anderson, K. C.; Richardson, P. G. *Cl. Lymph. Myelom. Leuk.* **2011**, *11*, 17.
46. Kimura, T.; Iwatsuki, M.; Asami, Y.; Ishiyama, A.; Hokari, R.; Otoguro, K.; Matsumoto, A.; Sato, N.; Shiomi, K.; Takahashi, Y.; Omura, S.; Nakashima, T. *J. Antibiot.* **2016**, *69*, 818. http://dx.doi.org/10.1038/ja.2016.28
47. Heffner, R. J.; Jiang, J.; Joullie, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 10181. http://dx.doi.org/10.1021/ja00052a015
48. Jacobsen, O.; Klaveness, J.; Rongved, P. *Molecules* **2010**, *15*, 6638. http://dx.doi.org/10.3390/molecules15096638
49. Yu, X.; Sun, D. *Molecules* **2013**, *18*, 6230. http://dx.doi.org/10.3390/molecules18066230
50. Liu, X.; Sternberg, E.; Dolphin, D. *J. Org. Chem.* **2008**, *73*, 6542. http://dx.doi.org/10.1021/jo8007989
51. Mang, S. L.; Grubbs, R. H. *Chem. Sci.* **2015**, *6*, 4561. http://dx.doi.org/10.1039/c5sc01507c
52. Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *106*, 6086. http://dx.doi.org/10.1002/anie.200600641
53. Scheiper B.; Glorius F.; Leitner A.; Fürstner A. PNAS **2004**, 11960. http://dx.doi.org/10.1073/pnas.0401322101
54. Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock R. R.; Hoveyda A. H. *Chem. Eur. J.* **2013**, *19*, 2726. http://dx.doi.org/10.1002/chem.201204045

55. Wang Y.; Jimenez M.; Sheehan P.; Zhong C.; Hung A. W.; Tam C. P.; Young D. W. *Org. Lett.* **2013**, *15*, 1218.
http://dx.doi.org/10.1021/ol400134d
56. Majumdar K. C.; Rahaman H.; Roy B. *Curr. Org. Chem.* **2007**, *11*, 1339.
http://dx.doi.org/10.2174/138527207782023166
57. Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2008**, *73*, 1270.
http://dx.doi.org/10.1021/jo702092x
58. Prabhakaran, E. N.; Rao, N.; Boruah, A.; Iqbal, J. *J. Org. Chem.* **2002**, *67*, 8247.
http://dx.doi.org/10.1021/jo0200320
59. Banerji, B.; Mallesham, B.; Kumar, S. K.; Kunwar, A. C.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6479.
http://dx.doi.org/10.1016/s0040-4039(02)01239-x
60. Harris, P. W. R.; Brimble, M. A.; Gluckman, P. D. *Org. Lett.* **2003**, *11*, 1847.
http://dx.doi.org/10.1021/ol034370e

