

An improved synthesis of a ring-C precursor to cobyric acid

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Dedicated to Professor James M. Cook on the occasion of his 65th birthday

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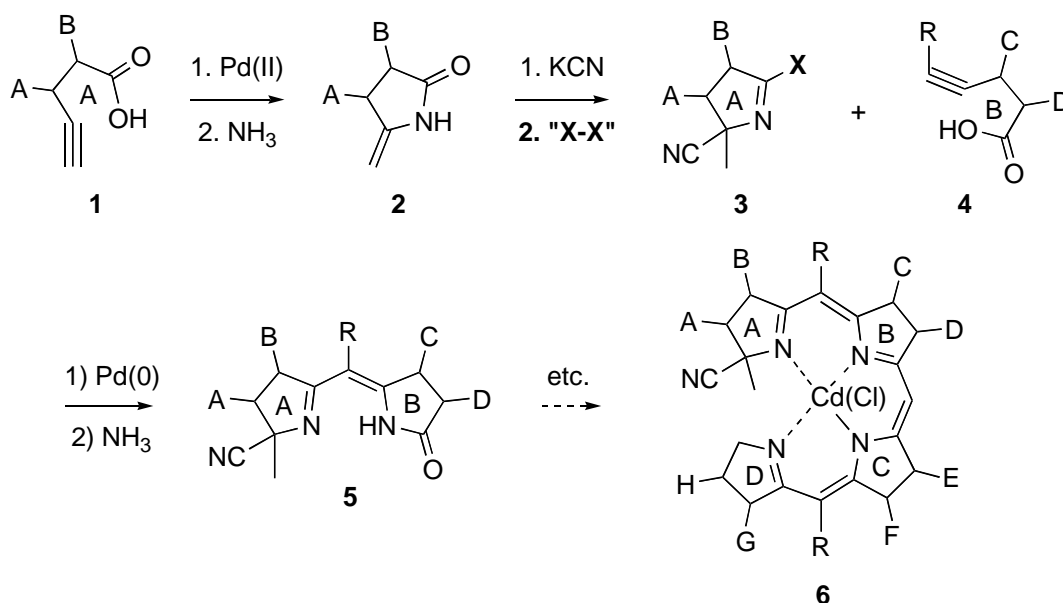
Abstract

Alkyne acid **10** was prepared in enantioselective fashion from allylic ester derivative (*R*)-**18** via an *E*-selective Ireland-Claisen rearrangement followed by Si-assisted elimination of HBr. The present route offers significant advantages in terms of both scalability and overall yield compared to that previously described. Alkyne acid **10** is an attractive ring-C precursor for an ongoing synthesis of cobyric acid.

Keywords: Cobyric acid, 4-pentynoic acids, Ireland-Claisen rearrangement, (–)-DIP-Cl

Introduction

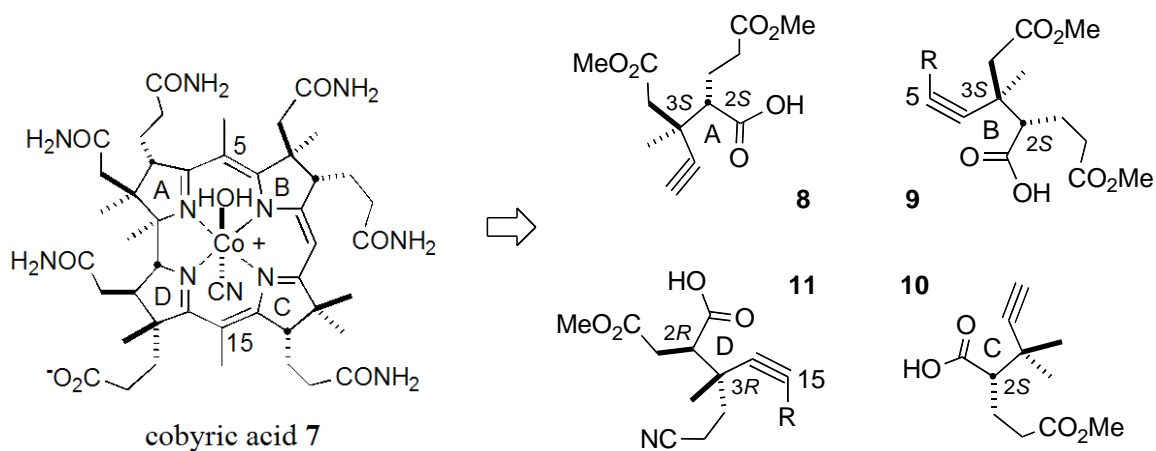
For some time we have been developing an iterative synthesis of semicorrins of type **5** and higher homologues, in which the pyrroline and lactam rings are derived from suitably functionalized alkyne acids (Scheme 1).¹ Alkyne acids **1** are first converted to imidoyl



Scheme 1. An iterative synthesis of semicorrins and higher homologues.

chlorides or triflates **3** by a four step sequence consisting of (1) Pd(II)-catalyzed cyclization; (2) aminolysis of the resultant enolactone to give lactam **2**; (3) enamide protection (KCN); and (4) lactam activation employing either CCl₄/PPh₃ (X = Cl) or Tf₂O/imidazole (X = OTf). Imidoyl derivatives **3** are then transformed to semicorrins **5** by Pd(0)-mediated coupling-cyclization with alkyne acids **4**, followed by aminolysis (R = H, Me). In analogous fashion, repetition of this cycle with **5** affords tri- and tetrapyrrole derivatives. Furthermore, semicorrins **5** are themselves versatile building blocks for a variety of pyrrole-derived natural products. For example, condensation of **5** with a similarly derived C,D-ring dipyrin provides direct access to *seco*-corrins **6**, which are properly functionalized for photochemical ring closure to produce corrins. Eschenmoser et al. pioneered this route to corrins in their elegant syntheses of cobyrinic acid **7** and vitamin B₁₂.²

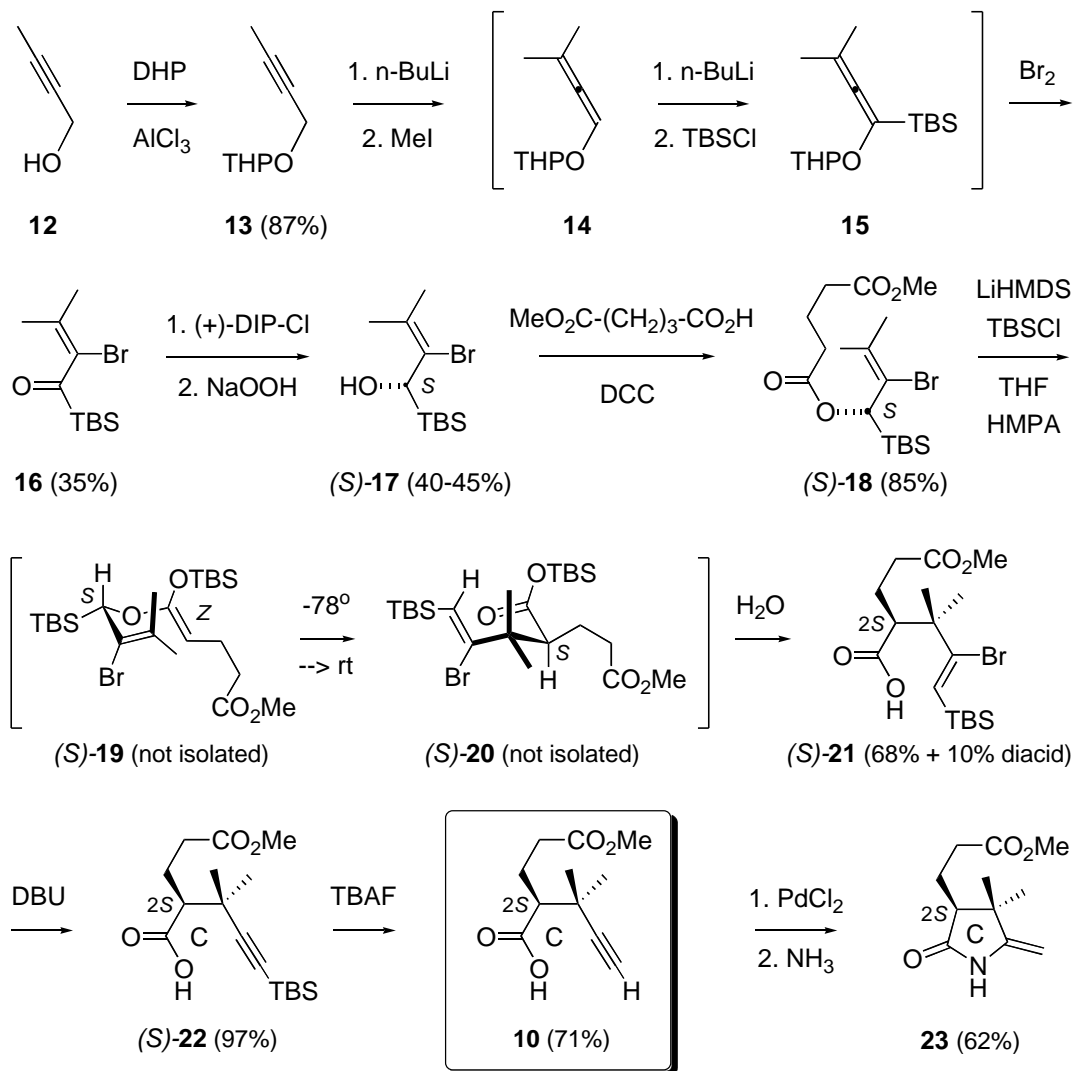
We are in the process of extending our alkyne acid methodology to the synthesis of **7**, which requires a ready source of homochiral A-D ring precursors **8–11** (Scheme 2). Linking of these fragments as described above would then afford a fully functionalized *seco*-corrin precursor to **7**, corresponding in structural features to **6**.



Scheme 2. Proposed synthesis of cobyric acid **7**.

Results and Discussion

In earlier studies we described an enantioselective synthesis of the ring-C precursor **10**, a key step of which was an Ireland-Claisen rearrangement of the homochiral allylic ester (*S*)-**18** (Scheme 3).^{1b} This material was prepared in modest overall yield beginning with 2-butyne-1-ol **12**, which was first converted into the THP derivative **13** by AlCl₃-catalyzed condensation with dihydropyran. Our plan then called for conversion of **13** to the TBS-ketone **16** (TBS = *t*-butyl-dimethylsilyl) following the general protocol of Reich et al.³ This involved sequential alkylation of **13** with MeI followed by TBSCl to generate an intermediate allene derivative **15**, which without purification was subjected to bromination at $-78\text{ }^{\circ}\text{C}$ in dichloromethane. In this manner we were able to obtain up to 35% yields of the desired intermediate **16**, which provided sufficient material for further experimentation. We next screened a wide variety of reagents for effecting the enantioselective reduction of **16** to (*S*)-**17**, the most satisfactory of which turned out to be (+)-DIP-Cl.⁴ Even this reagent was not without its drawbacks, however. Thus, although (*S*)-**17** was obtained with an ee >95%, experimental difficulties with the NaOH/HOOH cleavage procedure precluded its isolation in better than 45% yield. In the event, DCC-mediated coupling of (*S*)-**17** with *mono*-methyl glutarate gave an 85% yield of the desired allylic ester (*S*)-**18**, which was carried on to the subsequent Ireland-Claisen rearrangement step.⁵

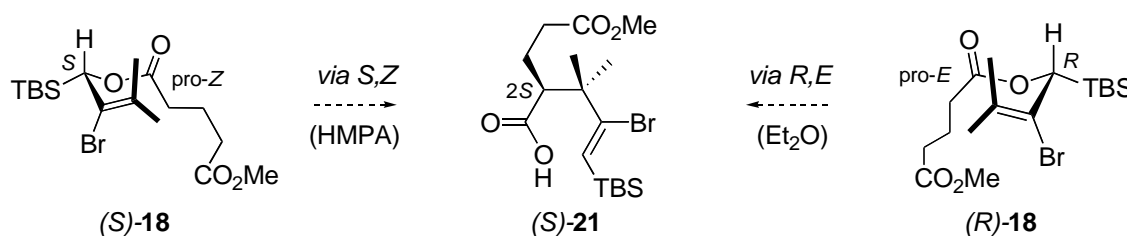


Scheme 3. Previous synthesis of ring-C precursor **10**.

The *t*-butyldimethylsilyl (TBS) group in **(S)-18** served two roles: (1) as a proton surrogate providing the chirality necessary for inducing the *S*-configuration at C-2 in **10**; and (2), as an anchor for stabilizing the desired chair conformation leading from **(S)-18** to **(S)-21**. In practice, the combination of *S*-configuration at the allylic ester and *Z*-enolate geometry in **(S)-19** afforded carboxylic acid **(S)-21** in 60–70% yield (and 10% of the corresponding diacid), with ee >95%.^{1b} Alkene **(S)-21** was then converted directly into the desired alkyne acid **10** by Si-assisted elimination of HBr, followed by TBS cleavage. Finally, the structure of **10** was confirmed by its two-step conversion to the known cyclic enamide **23**, previously employed by Eschenmoser in his synthesis of cobyric acid **7**.²

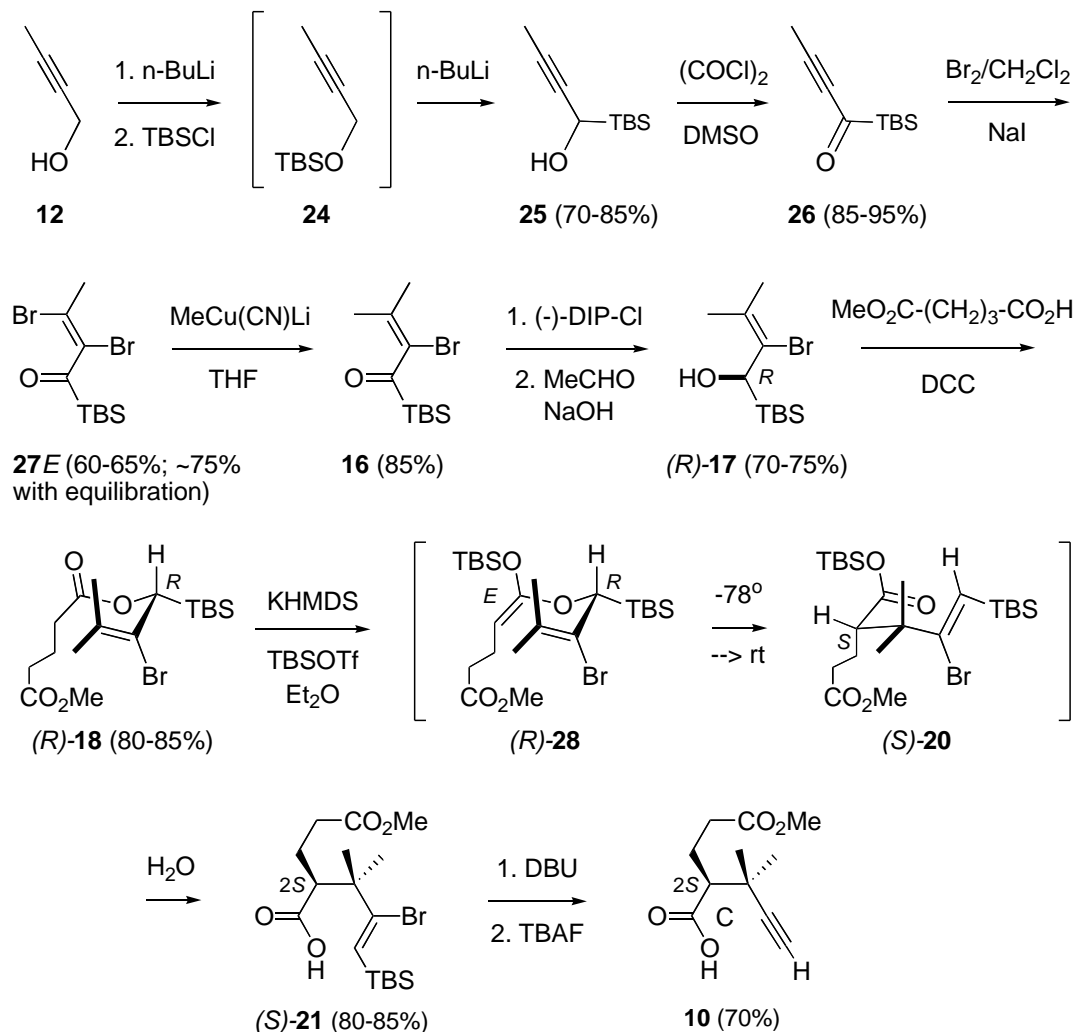
While workable, this route to **10** had a number of problems that led us to re-investigate its synthesis. Among these, the low yields in the conversion of **13** to **16**, and subsequently of **16** to **(S)-17** represented a significant bottleneck. Also, the key Ireland-Claisen rearrangement leading

from (*S*)-**18** to (*S*)-**21** was difficult to scale, and invariably produced 10-15% of the diacid corresponding to (*S*)-**21**. Finally, the necessity of employing carcinogenic HMPA as an additive to generate the *Z*-silylenolate of (*S*)-**18** raised safety concerns. To address this last issue, we set out to explore the possibility of effecting an *E*-selective ester-silylenolate rearrangement on allylic ester (*R*)-**18**, the optical antipode of (*S*)-**18**, as an alternative means of establishing the 2*S*-configuration in (*S*)-**21** (Scheme 4). An important advantage to this route is that *E*-silylenolate formation is typically carried out in non- or weakly coordinating solvents such as diethyl ether, eliminating the need for HMPA as an additive. Counterbalancing this advantage, however, *E*-selectivity is often more difficult to attain.



Scheme 4. An alternative pathway to (*S*)-**21**.

To evaluate this strategy it was first desirable to develop a more efficient synthesis of the TBS-ketone **16**, an intermediate common to both the (*S*)-**18** (via *Z*-enolate) and (*R*)-**18** (via *E*-enolate) routes. As in our previous studies (cf. Scheme 3), this was accomplished beginning with commercially available 2-butyne-1-ol **12**, but in much more efficient fashion (Scheme 5). Following a literature procedure,⁶ **12** was first silylated employing *n*-BuLi/TBSCl, and the resulting silyl ether **24** was subjected to in situ *retro*-Brook rearrangement to produce TBS-alcohol **25** in 70–85% yield. Swern oxidation of **25** then gave an 85–95% yield of the corresponding alkyne **26**. Our plan was that **26** would undergo selective *anti*-bromination to afford the *E*-dibromoketone (*E*)-**27**, for which there was some precedent.⁷ Initially, however, this reaction presented difficulties, in that under kinetic control the undesired *Z*-isomer predominated. For example, bromination of **26** at -78 °C (CH₂Cl₂/Br₂) gave a ~3:5 mixture of (*E*)-**27** and (*Z*)-**27**. In contrast, higher temperatures appeared to favor thermodynamic control, with the best results obtained at r.t. and in the presence of catalytic NaI. Under these conditions the desired *E*-isomer predominated by >2:1, and isolated yields of (*E*)-**27** ranged from 60–65% (vs. 25–30% for (*Z*)-**27**). Moreover, nearly the identical ratio of (*E*)-**27**:(*Z*)-**27** was obtained upon equilibration of isolated (*Z*)-**27** with BF₃·Et₂O at room temperature, raising the effective yield of (*E*)-**27** to ~75% after one recycle.^{1c} In this way we were able to conveniently prepare multigram quantities of (*E*)-**27** for subsequent conversion to TBS-ketone **16**. This was accomplished upon treatment of (*E*)-**27** with MeCu(CN)Li/THF in 85% yield. The overall yield following this route to **16** was ~45%, a significant improvement over that previously described (~30%; Scheme 3).



Scheme 5. Improved synthesis of ring-C precursor **10**.

With ample quantities of **16** now in hand, we devoted considerable effort to effecting the asymmetric reduction of **16** to give **(R)-17**. From among many reagent combinations screened, (–)-DIP-Cl provided the highest ee's (~95%). However, as previously observed for **(S)-17** (cf. Scheme 3), overall yields for this step were only fair (40–45%), in part due to the harsh conditions involved in cleaving the product from the initial boron-oxygen adduct (HOOH/NaOH, or diethanolamine^{8a}). In addition, however, we observed a marked concentration effect on this reaction, which led us to explore Brown's modified reduction and cleavage conditions for sterically hindered ketones.^{8b} Following this protocol, treatment of **16** with neat (–)-DIP-Cl afforded a viscous mixture after stirring 36 h at r.t., which on cleavage with acetaldehyde, followed by NaOH, afforded 70–75% yields of alcohol **(R)-17** with ee ~95%. Finally, **(R)-17** underwent smooth coupling with *mono*-methyl glutarate to afford the desired allylic ester **(R)-18** in 80–85% yield.

We had now reached the point of effecting the *E*-selective Ireland-Claisen rearrangement of (*R*)-**18**, which turned out to be only moderately selective employing common literature conditions.⁵ These results mirror those we obtained previously with a related system.^{1c} Gratifyingly, however, excellent selectivity was achieved employing a slight modification of conditions recently reported by McIntosh et al.⁹ Adapting this methodology, *E*-enolate formation was carried out with freshly prepared KHMDS and TBSOTf in Et₂O at -78 °C. Following warming to r.t., and aqueous hydrolysis, alkene acid (*S*)-**21** was obtained in 80–85% yields. The material thus obtained was identical in all respects to (*S*)-**21** prepared as described in Scheme 3, and was produced in ~25% overall yield from 2-butyne-1-ol **12**. Finally, as described previously,^{1b} (*S*)-**21** was readily converted into the ring-C precursor **10** by DBU-mediated dehydrobromination followed by de-silylation.

Conclusions

The described synthesis of (*S*)-**21** represents an approximately three-fold increase in yield compared to our previous route (~25% vs ~8%), and of equal importance, eliminates the need for HMPA. We anticipate that similar methodology can be employed for the syntheses of the A, B ring precursors **8** and **9**.

Experimental Section

General. TLC was performed on pre-coated 250 μm silica 60 F₂₅₄ glass-backed plates. Flash chromatography was performed using Rf grade silica (60 Å, 200–400 mesh) or neutral alumina (Grade III, 58 Å, 150 mesh). ¹H and ¹³C NMR spectra were recorded at 300 or 500 MHz. Unless otherwise stated, CDCl₃ was used as the solvent. Resonances were reported in parts per million downfield from TMS and were referenced to either the residual solvent peak (¹H; CHCl₃: δ 7.27) or the solvent resonances (¹³C; CDCl₃: δ 77.23). Elemental analyses were performed by Atlantic Microlab Inc., and high resolution mass spectrometry was performed at the University of Illinois Urbana-Champaign Mass Spectrometry Laboratory.

1-(*tert*-Butyldimethylsilyl)but-2-yn-1-ol (25). This material was prepared by a modification of a known procedure:⁶ A solution of 2-butyne-1-ol (**12**; 3.0 mL, 40.1 mmol, 1.0 equiv.) in anhydrous THF (60 mL) was stirred in a 250 mL round bottom flask at -78 °C (dry ice/acetone) under argon. To this solution was slowly added *n*-BuLi (2.5 M; 16.8 mL, 42.1 mmol, 1.05 equiv.) via cannula. The solution was then stirred at 0 °C (ice water bath) for 30 min. The vessel was then re-cooled to -78 °C (dry ice/acetone) and, once cooled, TBSCl (1.0 M in THF; 42.1 mL, 42.1 mmol, 1.05 equiv.) was added. The resulting solution was warmed to r.t. and stirred for 4 h. At this time the reaction was cooled to -78 °C (dry ice/acetone) and *n*-BuLi (2.5 M in

hexanes; 19.0 mL, 48.12 mmol, 1.2 equiv.) was slowly added via cannula. The solution was then warmed to $-45\text{ }^{\circ}\text{C}$ (dry ice/acetonitrile) and stirred for 2 h. Lastly, the solution was cooled to $-78\text{ }^{\circ}\text{C}$ (dry ice/acetone) and quenched with AcOH (10% in THF; 60 mL). The solution was then diluted with Et₂O and washed sequentially with H₂O and brine, dried over MgSO₄, and concentrated. Purification on silica gel (hexane/EtOAc) gave the known product **25** (5.15 g, 73%) as a colorless oil. *R_f* 0.25 (hexane/EtOAc 20:1). ¹H-NMR (500 MHz, CDCl₃): δ 4.11 (q, 2.7 Hz, 1H), 1.80 (d, 2.7 Hz, 3H), 0.90 (s, 9H), 0.03 (s, 3H), -0.002 (s, 3H). ¹³C-NMR (500 MHz, CDCl₃): δ 83.69, 80.50, 54.73, 26.94, 16.97, 3.84, -7.90 , -8.53 .

1-(tert-Butyldimethylsilyl)but-2-yn-1-one (26). This material was prepared following a modification of a known procedure.⁶ A solution of oxalyl chloride (2.0 M in CH₂Cl₂; 15.3 mL, 30.6 mmol, 2.0 equiv.) in dry CH₂Cl₂ (54 mL) was stirred in a 250 mL round bottom flask at $-78\text{ }^{\circ}\text{C}$ under argon. To this solution was added dry DMSO (4.34 mL, 61.2 mmol, 4.0 equiv.) (**warning**: keep cold). While at $-78\text{ }^{\circ}\text{C}$, a solution of alcohol **12** (2.82 g, 15.3 mmol, 1.0 equiv.) in CH₂Cl₂ (15 mL) was added dropwise. Lastly, dry Et₃N (10.6 mL, 76.5 mmol, 5.0 equiv.) was added. The reaction was then warmed to r.t. and stirred until complete by TLC (hexane/EtOAc 7:1). Upon completion (45 min), the solution was partitioned between saturated aqueous NH₄Cl and CH₂Cl₂. The organic portion was then washed with brine and dried over MgSO₄. Concentration, followed by purification on silica gel (hexane/EtOAc 10:1) gave the known ynone **26** (2.52 g, 91%) as a yellow oil. *R_f* 0.42 (hexane/EtOAc 20:1).⁶ ¹H-NMR (500 MHz, CDCl₃): δ 2.11 (3H, s), 0.98 (9H, s), 0.23 (6H, s).

(E/Z)-1-(tert-Butyldimethylsilyl)-2,3-dibromobut-2-en-1-one (E-27 and Z-27). A solution of ynone **26** (1.11 g, 6.10 mmol) in CH₂Cl₂ (10 mL) was treated with NaI (92 mg, 0.61 mmol, 0.1 equiv.). The resulting suspension was treated dropwise, with efficient stirring, with Br₂ (1.03 g, 6.44 mmol, 1.06 equiv.). After addition was complete, the reaction was stirred for an additional 20 min, then poured into Na₂S₂O₃ solution (20%; 20 mL) and extracted with CH₂Cl₂ (3x15 mL). The organic extracts were combined, washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford a yellow oil. Flash chromatography (silica gel, hexanes) afforded (*E*)-**27** (1.30 g, 62%) and (*Z*)-**27** (0.57 g, 27%), both as yellow oils. (*E*)-**27**: *R_f* 0.59 (silica gel, hexanes/EtOAc 20:1). IR (thin film): ν 2930, 1641, 1250 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 0.32 (s, 6H), 1.00 (s, 9H), 2.46 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ -5.39 , 17.3, 26.8, 27.2, 113.8, 117.9, 232.4. HRMS (ESI): Calcd. for C₁₀H₁₉Br₂OSi: 340.9572; found: 340.9577.

(*Z*)-**27**. *R_f* 0.70 (silica gel, hexanes/EtOAc 20:1). IR (thin film): ν 2930, 1636, 1576, 1251 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 0.30 (s, 6H), 0.98 (s, 9H), 2.39 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ -5.04 , 17.5, 26.7, 26.8, 127.3, 127.7, 231.0. HRMS (ESI): Calcd. for C₁₀H₁₉Br₂OSi: 340.9572; found: 340.9583.^{1c}

(E)-1-(tert-Butyldimethylsilyl)-2,3-dibromobut-2-en-1-one (E-27) by equilibration of (*Z*)-**27**. A solution of enone (*Z*)-**27** (4.98 g, 14.5 mmol) in CH₂Cl₂ (140 mL) was treated with BF₃·OEt₂ (0.41 g, 2.9 mmol, 0.2 equiv.) under nitrogen. The resulting solution was stirred at r.t. for 24 h, and then poured into saturated NaHCO₃ solution (80 mL). The organic layer was separated and

washed with $\text{Na}_2\text{S}_2\text{O}_3$ (20%; 80 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to afford a brown oil. Flash chromatography (silica gel, hexanes) afforded enone (*E*)-**27** (3.34 g, 67%) and enone (*Z*)-**27** (1.64 g, 33%), both as yellow oils, having identical spectral data as described above.^{1c}

2-Bromo-1-(tert-butyldimethylsilyl)-3-methyl-but-2-en-1-one (16). A solution of CuCN (2.04 g, 22.7 mmol; 4.0 equiv.) in THF (85 mL) was cooled to $-78\text{ }^\circ\text{C}$ under N_2 , and was treated dropwise, and with efficient stirring, with MeLi /hexanes (1.6 M; 14.2 mL, 22.7 mmol; 4.0 equiv.). After addition was complete, the reaction was allowed to warm to r.t. for 10 min to give a clear solution, and was then cooled back to $-78\text{ }^\circ\text{C}$. The reaction was then treated dropwise with a solution of *E*-dibromoene (*E*)-**27** (1.94 g, 5.68 mmol; 1.0 equiv.), while maintaining a temperature of $-78\text{ }^\circ\text{C}$. After addition was complete, the reaction was stirred at $-78\text{ }^\circ\text{C}$ for an additional 3 h and was then quenched with saturated NH_4Cl and allowed to warm to r.t. The aqueous solution was then extracted with EtOAc , and the combined extracts were washed sequentially with 1 M HCl , H_2O , saturated NaHCO_3 and brine. After drying over Na_2SO_4 , the extracts were concentrated under reduced pressure and the residue purified by flash chromatography (silica gel, 1% EtOAc /hexanes) to afford **16** (1.32 g, 85%) as a yellow oil, identical in all respects with material prepared as described in Scheme 3.^{1b}

(R)-(-)-2-Bromo-1-(tert-butyldimethylsilyl)-3-methyl-but-2-en-1-ol (R-17). In a flame dried round bottom flask, enone **16** (1.13 g, 4.06 mmol; 1 equiv.) was treated with (-)-DIP-Cl (1.56 g, 4.7 mmol; 1.2 equiv.) under N_2 , and the resulting mixture was stirred at r.t. for 36 h. Excess (-)-DIP-Cl was then removed under reduced pressure, first on a rotary evaporator and then under high vacuum. The residue was dissolved in Et_2O (7.50 mL) and treated with CH_3CHO (0.250 g, 5.68 mmol, 1.4 equiv.) at $0\text{ }^\circ\text{C}$, and the resulting mixture was stirred at r.t. for 4 h. At the end of this period, the reaction was treated with 6 N NaOH (15 mL), and stirring was continued for an additional 45 min.^{8b} The reaction was then extracted with Et_2O , and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 3% EtOAc /hexanes) to afford (*R*)-**17** (0.82 g, 70%) as a pale yellow oil. $[\alpha]_{\text{D}}^{23} = -11.6^\circ$ ($c = 1.2$, CHCl_3), having identical spectral data as that previously reported for (*S*)-**17**.^{1b}

(R)-(-)-2-Bromo-1-(tert-butyldimethylsilyl)-3-methyl-but-2-enyl methyl pentanedioate (R-18). In a flame dried round bottom flask, a solution of alcohol (*R*)-**17** (915 mg, 3.28 mmol, 1 equiv.) and *mono*-methyl glutarate (575 mg, 3.94 mmol, 1.2 equiv.) in CH_2Cl_2 (49 mL) was treated with DMAP (40 mg, 0.33 mmol, 0.1 equiv.) and DCC (813 mg, 3.94 mmol, 1.2 equiv.). The reaction mixture was then stirred at r.t. for 24 h, and the resulting suspension was filtered to remove dicyclohexylurea, which was washed with additional CH_2Cl_2 . The filtrate was then washed with 1.0 M HCl and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (silica gel, 3% EtOAc /hexanes) to afford (*R*)-**18** (1.09 g, 82%) as a colorless oil. $[\alpha]_{\text{D}}^{23} = -23.9^\circ$ ($c = 1.0$, CHCl_3), having identical spectral data as that previously reported for (*S*)-**18**.^{1b}

(S)-(+)-2-[2-Bromo-3-(tert-butyldimethylsilyl)-1,1-dimethylallyl] methyl pentanedioate (S-21). In a flame dried round bottom flask, a solution of allylic ester (*R*)-**18** (880 mg, 2.16 mmol, 1.0 equiv.) in Et₂O (24.0 mL) was treated with a solution of TBSOTf (2.28 g, 8.64 mmol, 4.0 equiv.) in Et₂O (13 mL) at -78 °C. After stirring an additional 5 min, a solution of freshly prepared KHMDS (1.81 g, 8.64 mmol, 4.0 equiv.) in THF (13 mL) was added portionwise. The resulting mixture was stirred at -78 °C for 30 min, then warmed slowly to r.t. over a period of 1 h, and stirred at r.t. for an additional 1 h. The reaction was then acidified with 1 M HCl to pH <2 and stirred overnight. The resulting solution was extracted with Et₂O and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was chromatographed (silica gel, 10% EtOAc/hexanes/1% HOAc) to afford (*S*)-**21** (715 mg, 81%) as a colorless oil. $[\alpha]_D^{23} = +0.72^\circ$ (c = 0.95, CHCl₃), having identical spectral data as that previously reported.^{1b} For the conversion of this material to ring-D precursor **10** see reference 1b.

Acknowledgements

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References

1. (a) For a discussion of this strategy see Jacobi, P. A.; Liu, H. *J. Org. Chem.* **2000**, *65*, 7676, and references therein. (b) Jacobi, P. A.; Tassa, C. *Org. Lett.* **2003**, *5*, 4879. (c) Wang, H.; Tassa, C.; Jacobi, P. A. *Org. Lett.* **2008**, *10*, 2837.
2. Eschenmoser, A.; Wintner, C. E. *Science* **1977**, *196*, 1410.
3. Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949.
4. Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16.
5. Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650, and references cited therein.
6. Sakaguchi, K.; Fujita, M.; Suzuki, H.; Higashino, M.; Ohfuné, Y. *Tetrahedron Lett.* **2000**, *41*, 6589.
7. Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997.
8. (a) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (b) Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379.
9. McFarland, C.; Hutchison, J.; McIntosh, M.C. *Org. Lett.* **2005**, *7*, 3641, and references therein.