Improved preparation of racemic 1,2,3,6,7,8,11,12,13-nonamethoxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene

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Abstract

Racemic 1,2,3,6,7,8,11,12,13-nonamethoxy-10,15-dihydro-5*H*-trbibenzo [*a,d,g*] cyclononene was prepared via trimerization of 3,4,5-trimethoxybenzyl alcohol catalyzed by Lewis acids such as $AlCl_3$, $ZnCl_2$, $FeCl_3$ and $SnCl_4$ in chlorinated solvents. The reaction proceeded smoothly in dichloromethane with $SnCl_4$ as catalyst and gave 54% yield. Some open chain oligomers were also obtained.

Keywords: Cyclotriveratrylene, trimerization, 3,4,5-trimethoxybenzyl alcohol, Lewis acid

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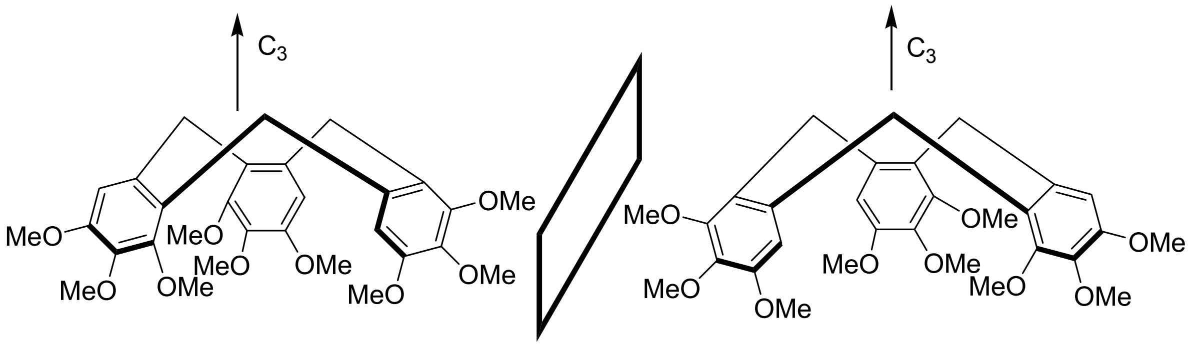
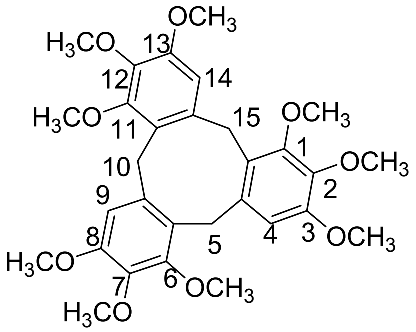
Introduction

Functionalized cyclotriveratrylenes (CTV), also referred as tribenzocyclononene (TBCN), have attracted much attention because of their rigid cone shaped frame and chiroptical properties.[1–2] 1,2,3,6,7,8,11,12,13-Nonamethoxy-10,15-dihydro-5*H*-trbibenzo[*a,d,g*]cyclononene (NDTC) was first isolated when Bosh attempted to couple 3,4,5-trimethoxybenzylmagnesium chloride and 1,3,4-trimethylpyridium iodide.[3] This molecule exhibits C_3 symmetry and is chiral (Figure 1).[4] The resolution of racemic NDTC has not been reported, but the structure was determined by X-ray crystallographic analysis and the racemic mixture was discriminated by ^{1}H-NMR using chiral shift reagents.[4,5] NDTC is usually prepared by trimerization of 3,4,5-trimethoxybenzyl alcohol in the presence of H_2SO_4 (aq.)[1] or bentonite-clay[6] with yields less than 12%.



M enantiomer *P* enantiomer

Figure 1. Structure of NDTC.



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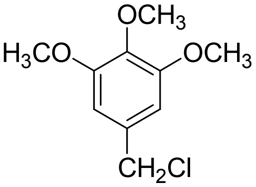

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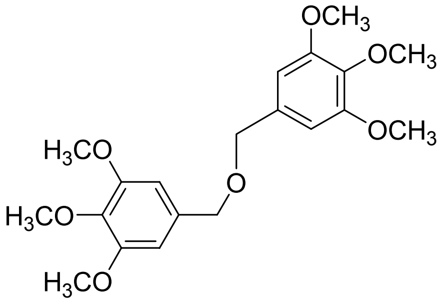

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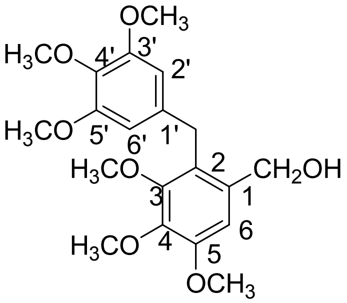

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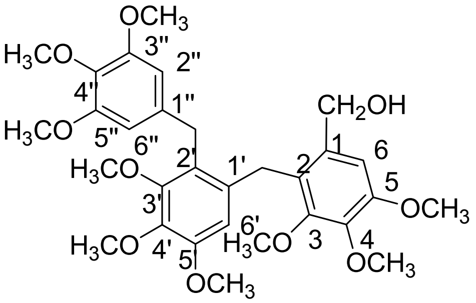

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Figure 2. Compounds derived from 3,4,5-trimethoxybenzyl alcohol in the presence of $AlCl_3$.

Results and Discussion

In our attempt to couple 3,4,5-trimethoxybenzyl acetate and benzoyl chloride in the presence of $AlCl_3$ in CH_2Cl_2, NDTC was obtained in 20% yield. Under the same reaction conditions, methyl 3,4,5-trimethoxybenzyl ether or benzyl 3,4,5-trimethoxybenzyl ether could also be cyclized to NDTC. When 3,4,5-trimethoxybenzyl alcohol was used directly, NDTC and some other compounds such as **2**, **3**, **4** and **5** were obtained (Figure 2). The reaction may proceed through the intermediate generated from benzyl alcohol with $AlCl_3$, leading to **2**, **3**, **4, 5** and eventually NDTC.

Further study indicated that 2 equivalent $AlCl_3$ is optimal for the synthesis of NDTC, whereas the yields are not significantly different at 20°C 10 °C, 0 °C or - 10 °C and - 20 °C. Many other Lewis acids, such as $ZnCl_2$, $FeCl_3$ and $SnCl_4$ could catalyze the trimerization. $SnCl_4$ gave the highest yield (54%) (**Table 1**). $TiCl_4$ did not catalyze the trimerization and gave 3,4,5-trimethoxybenzyl chloride as major product in a yield of 60%.

Table 1. Trimerization of 3,4,5-trimethoxybenzyl alcohol in the presence of Lewis acids*

Entry	Lewis acids	Isolated yields (%)
1	$AlCl_3$	24%
2	$ZnCl_2$	29%
3	$FeCl_3$	22%
4	$TiCl_4$	trace
5	$SnCl_4$	54%

*Carried out in CH_2Cl_2 at rt. with 2 eq. Lewis acids. The reaction was quenched with water when the alcohol had been consumed.

Table 2. Effects of solvents on the trimerization of 3,4,5-trimethoxybenzyl alcohol*

Entry	Solvent	Isolated yield (%)
1	CH_2Cl_2	54%
2	$ClCH_2CH_2Cl$	47%
3	$CHCl_3$	49%
4	CCl_4	40%
5	CH_3CCl_3	29%
6	CS_2	trace
7	CH_3NO_2	20%

*Carried out at rt. with 2 eq. $SnCl_4$. The reaction was quenched with water when the alcohol had been consumed.

$SnCl_4$ was selected to investigate the effect of solvents. The results showed that chlorinated solvents are suitable for the reaction except CH_3CCl_3 (Table 2.)

Experimental Section

General Procedures Melting points were determined using an XRC-1 melting point apparatus (Sichuan University Science Instruments Factory) and are uncorrected. IR spectra were carried out on a Perkin Elmer Spectrum One spectrometer. Mass spectra were obtained on a Finnigan - LCQ^{DECA} mass spectrometer (ESIMS) and VG7070E mass spectrometer (EIMS). NMR spectra were recorded on a Bruker Avance 600 spectrometer with TMS as internal standard. 3,4,5-Trimethoxybenzyl alcohol was synthesized from reduction of methyl 3,4,5-trimethoxybenzoate with $LiAlH_4$ in 85% yield. [7] All commercial reagents were purified according to the reported procedures[8] prior to use.

General procedure for the synthesis of NDTC

To the solution of 3, 4, 5-trimethoxybenzyl alcohol (198 mg, 1 mmol) in 20 ml solvent was added 2.0 equivalent Lewis acid. The mixture was stirred at room temperature until completion (about 0.5 h, monitored by TLC). The reaction mixture was then poured into ice water, the aqueous layer was separated and extracted with chloroform (2×10 ml). The organic layers were combined and washed successively with 1 mol/L HCl, water and brine, dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum and the residue was subjected to silica gel column eluted with petrol/ethyl acetate (10:1) to give NDTC. NDTC was obtained as colorless needles after recrystallization from ethyl acetate.

1,2,3,6,7,8,11,12,13-Nonamethoxy-10,15-dihydro-5*H*-trbibenzo [*a,d,g*] cyclononene (1). Colorless needles; mp 198-200°C (lit[5] 200-203°C); ESIMS (positive mode) *m/z*: 563 $[M+Na]^+$; HRESIMS (positive mode) *m/z*: 563.2252 ($[M+Na]^+$, calcd for $C_{30}H_{36}O_9Na$, 563.2257); IR (KBr) ν_{max} cm^{-1}: 3010, 2931, 2829, 1599, 1580, 1492, 1449; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.24 (s, 3H), 4.42 (d, 3H, J = 13.6 Hz), 4.03 (d, 3H, J = 13.6 Hz), 3.97 (s, 9H), 3.80 (s, 9H), 3.77 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 151.5, 151.4, 140.4, 136.2, 125.5, 110.3, 60.6, 60.5, 55.7, 29.9.

3,4,5-Trimethoxybenzyl chloride (2). Colorless powder; mp 60-61 °C (lit[9] 60-62°C); EIMS *m/z*: 216(42%), 181(100%); IR (KBr) ν_{max} cm^{-1}: 2965, 2924, 2850, 1593, 1506, 1456; ^1H NMR (600MHz, $CDCl_3$) δ: 6.62 (s, 2H), 4.55 (s, 2H), 3.89 (s, 6H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 153.3, 138.1, 132.9, 105.7, 60.9, 56.2, 46.8.

Bis (3,4,5-trimethoxybenzyl) ether (3). Oil, EIMS *m/z*: 378 (6%), 182 (100%), 167 (20%) ; IR (film) ν_{max} cm^{-1}: 2941, 2839, 1593, 1507, 1462; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.59 (s, 4H), 5.03 (s, 4H), 3.87 (s, 12H), 3.84 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 153.3, 137.9, 131.4, 105.6, 66.6, 60.8, 56.1.

3,4,5-Trimethoxy-2-(3,4,5-trimethoxybenzyl)benzyl alcohol (4). Oil, ESIMS (positive mode) *m/z*: 401 $[M+Na]^+$; HRESIMS (positive mode) *m/z*: 401.1557 ($[M+Na]^+$, calcd for $C_{20}H_{26}O_7Na$, 401.1571); IR (film) ν_{max} cm^{-1}: 3502, 3006, 2938, 2838, 1591, 1505, 1494, 1463; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.82 (s, 1H), 6.33 (s, 2H), 4.58 (s, 2H), 3.99 (s, 2H), 3.88 (s, 6H), 3.79 (s, 3H), 3.78 (s, 3H), 3.75 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 153.2, 152.3, 152.1, 141.7, 137.1, 136.1, 134.9, 124.1, 107.6, 105.0, 63.1, 61.1, 60.8, 60.7, 56.0, 55.9, 31.2.

3,4,5-Trimethoxy-2-(3,4,5-trimethoxy-2-(3,4,5-Trimethoxybenzyl) benzyl)benzyl alcohol (5). Oil, ESIMS (positive mode) *m/z*: 581 $[M+Na]^+$; HRESIMS (positive mode) *m/z*: 581.2359 ($[M+Na]^+$, calcd for $C_{30}H_{38}O_{10}Na$, 581.2357); IR (film) v_{max} cm^{-1}: 3499, 2924, 2851, 1590, 1490, 1458; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.80 (s, 1H), 6.41 (s, 2H), 5.98 (s, 1H), 4.24 (s, 2H), 4.11 (s, 2H), 3.88 (s, 3H), 3.86 (br s, 8H), 3.84 (s, 3H), 3.82 (s, 3H), 3.80 (s, 6H), 3.70 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 153.2, 152.5, 152.2, 152.1, 151.9, 141.6, 140.3, 136.9, 136.1, 135.5, 135.0, 124.2, 123.2,.107.6, 106.9, 105.2, 62.9, 61.2, 61.0, 60.9, 60.8, 56.1, 55.9, 55.7, 31.8, 28.0.

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