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Optically Active Trialkynyl(phenyl)methane: Synthesis and Determination of Its Absolute Configuration by Vibrational Circular Dichroism (VCD) and Optical Rotatory Dispersion (ORD)

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Both enantiomers of an optically active trialkynyl(phenyl)methane (the key building blocks in the construction of a stable expanded cubane) have been prepared. The strategy involved the resolution of a racemic intermediate by means of HPLC on a chiral stationary phase. The absolute configuration of this intermediate was unambiguously assigned by using vibrational circular dichroism (VCD) and optical rotatory dispersion (ORD), in combination with density functional theory (DFT) calculations.

Introduction

The geometrically defined expansion of molecules by insertion of buta-1,3-diyne-1,4-diyl fragments into C–C single bonds has been a topic of research in our group for nearly 20 years. This approach to new carbon-rich molecules has rendered a plethora of "expanded" polyacetylenes [the poly(triacetylene)s], arenes, annulenes, radialenes, and radiaannulenes.^[1] The application of this concept to the third dimension led to the synthesis of the first expanded cubane (EC), bearing methoxy groups as substituents in the corners (Figure 1a).^[2] The synthesis of the octamethoxy-EC consisted of the sequential construction of the corners, edges, and faces of the cube. Unfortunately, the use of racemic corner modules led to very low overall yield; a consequence of the formation of inseparable mixtures of diastereoisomers during the edge- and face-forming steps. To circumvent this problem, the synthesis of an optically active, asymmetrically silyl-protected methyl trialkynylmethyl ether was developed.^[3]



Figure 1. Expanded cubanes: (a) octamethoxy derivative; (b) octaphenyl derivative.

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A serious problem associated with octamethoxy-EC, which prevented production of larger materials quantities and full exploration of its physical properties, is its high instability: it explodes upon scraping. However, the stabilities of a series of expanded polyhedranes were investigated theoretically by using a combination of isodesmic, group additivity, and molecular mechanics methods.^[4] These stud-

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ies revealed that most of the strain energy rests in the relatively flexible buta-1,3-diyne-1,4-diyl edges, therefore expanded derivatives are in fact less strained, and structurally more stable than their unexpanded counterparts. In this sense, the unexpected instability of the octamethoxy-EC can be explained in terms of an alternate decomposition pathway. Mass spectrometry revealed the successive loss of up to eight methoxy groups in both the positive and negative ion mode, leading to the proposal of a polar mechanism involving highly unstable nonplanar tripropargyl ions.^[2] To hinder this decomposition pathway, a different substituent in the corner module is required. An alternative building block is a trialkynyl(phenyl)methane, as a precursor of an octaphenyl-EC (Figure 1b), which is expected to be more stable than the octamethoxy derivative.

Herein, we report the synthesis and optical resolution of an asymmetrically silyl-protected trialkynyl(phenyl)methane and the determination of its absolute configuration by vibrational circular dichroism (VCD)^[5] and optical rotatory dispersion (ORD).

Results and Discussion

The synthesis of the trialkynyl(phenyl)methane is depicted in Scheme 1. The initial step involved the cross-coupling of ethynyltriisopropylsilane (1) to ethyl 3-phenylpropiolate (2) in the presence of Pd(OAc)₂ and tris(2,6-dimethoxyphenyl)phosphane (TDMPP) to provide the enynoate 3 in high yield (84%).^[6] The next step was the reduction of ester 3 to alcohol 4 by using DIBAL-H in THF, followed by epoxidation with *m*-chloroperbenzoic acid (MCPBA) to afford the racemic epoxide (\pm) -5. At this stage, several asymmetric epoxidation procedures were tried to obtain 5 in optically pure form and high yields (see the Supporting Information); however, all of them proved to be strategically inconvenient. The racemic epoxy alcohol (\pm) -5 was protected by using $tBuMe_2SiCl$ to deliver derivative (±)-6. Compound (\pm) -6 underwent Yamamoto rearrangement^[7] in the presence of methylaluminum bis(4-bromo-2,6-di-tertbutylphenoxide) (MABR) to give aldehyde (\pm) -7. Corey-Fuchs dibromoolefination gave (\pm) -8, which was trans-



Scheme 1. Synthesis of optically pure trialkynyl(phenyl)methane. Reagents and conditions: (a) Pd(OAc)₂, TDMPP, benzene, 20 °C, 24 h, 84%; (b) DIBAL-H, THF, -78 °C, 3 h, 95%; (c) *m*-CPBA, Na₂HPO₄, CH₂Cl₂, 0 °C, 2 h, 75%; (d) *t*BuMe₂SiCl, imidazole, CH₂Cl₂, 0 - 20 °C, 24 h, 95%; (e) MABR, CH₂Cl₂, -78 °C, 45 min, 67%; (f) PPh₃, CBr₄, CH₂Cl₂, 0 °C, 3 h, 93%; (g) *n*BuLi, THF, -78 °C, 2 h, 95%; (h) TFA/H₂O (9:1), CH₂Cl₂, 0 °C, 45 min, 100%; (i) *n*BuLi, Me₃SiCl, THF, -78 °C, 2 h, then HCl 1 N, THF, -78 °C, 20 min, 72%; (j) DMP, CH₂Cl₂, 0 °C, 12 h, 74%; (k) PPh₃, CBr₄, CH₂Cl₂, 0 °C, 3 h, 83%; (l) *n*BuLi, THF, -78 °C, 3 h, 73%. TDMPP = tris(2,6-dimethoxyphenyl)phosphane, DIBAL-H = diisobutylaluminum hydride, *m*-CPBA = *m*-chloroperbenzoic acid, MABR = methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide), TFA = trifluoroacetic acid, DMP = Dess–Martin periodinane.

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formed into dipropargyl derivative (\pm) -9 in good yields.^[8] The key intermediate (\pm) -10 was obtained by removal of the SiMe₂/Bu protecting group. The enantiomers (+)-10 and (–)-10 were obtained in enantiomerically pure form after resolution by HPLC on a chiral stationary phase (WHELK-O1, for details see the Supporting Information). The last steps of the synthesis were the Dess–Martin oxidation of (+)-10 to give aldehyde (+)-11,^[9] a second Corey–Fuchs olefination to furnish the intermediate (–)-12, and subsequent elimination to yield the final compound (+)-13. The pure enantiomers (–)-11, (+)-12, and (–)-13 were obtained similarly by starting from (–)-10 (for experimental details, see the Supporting Information). Enantiomers (+)-13 and (–)-13 were obtained as colorless oils that are stable under ambient laboratory conditions.

Despite their high optical purity ($\geq 99\% ee$), compounds 10, 11, 12, and 13 featured electronic circular dichroism (ECD) spectra with very weak Cotton effects, which could not be distinguished from noise. This lack of Cotton effects in the measurable range precludes the determination of the absolute configuration by direct comparison of the calculated and experimental ECD traces.

Several derivatives of **10** were prepared in an attempt to determine the absolute configuration by X-ray crystallographic methods. Unfortunately, all these derivatives were oils, which could not be crystallized. Other attempts to couple strong chromophores, which could provide Cotton effects in the visible or near-UV range, failed.

In view of the impossibility of using ECD to determine the absolute configuration of these molecules, we decided to use a combination of VCD spectroscopy and ORD to determine the absolute configuration of compound 10.^[10] In order to obtain the calculated spectra, we performed a conformational search to identify the conformers that contribute to the equilibrium properties, and assess their populations in a Boltzmann ensemble (for details see the Supporting Information). The conformational search was performed by using a mixed Monte Carlo Multiple Minimum/ Low-Mode Conformational Search algorithm (for details see the Supporting Information), followed by geometry optimization of the resulting conformers at the B3LYP/6-31G(d) level of theory using Gaussian 03.[11] This further refinement led to the three main conformers shown in Figure 2. Their relative populations were determined by using the computed Gibbs free energy.

The VCD spectrum of alcohol **10** was measured in dry CCl_4 at a concentration of 0.14 M. Infrared spectroscopy shows only marginal association of **10** at this concentration (see the Supporting Information). VCD and ORD data were also calculated at the B3LYP/6-31G(d) level of theory. The VCD curve calculated for the ensemble of (*S*)-**10**,^[12] and the spectrum measured for (–)-**10** are shown in Figure 3. The calculated Cotton effects 1 and 2 correlate well in sign and frequency with the experimental ones. Cotton effects 3, 4, and 5 are shifted to higher wavenumbers, and the relative intensities of 4 and 5 are not well reproduced. Equivalent results were obtained when optimization and harmonic vibrational analysis (including VCD) were per-



Figure 3. Calculated IR (dashed line, upper graph), experimental IR (solid line, upper graph), calculated VCD (dashed line, lower graph), and experimental VCD spectrum (solid line, lower graph). Calculated frequencies were shifted by 0.97. For details and assignment of the Cotton effects, see the Supporting Information.



Figure 2. Conformers of (R)-10 found at the B3LYP/6-31G(d) level of theory. The conformer populations (Boltzmann distribution) were determined by using the computed Gibbs free energy at 298.15 K and 1 atm.



formed at the B3PW91/6-31G+(d) level of theory. Differences between calculated and experimental VCD spectra can be attributed to the omission of conformers with minor contributions, bad estimation of the conformer's free energy, functional and/or basis set effects, and even to experimental errors. However, the overall signature of the curve calculated for the (S) structure is in qualitative agreement with that measured for the (–) sample.

To support the assignment made by VCD, optical rotation values at four different wavelengths were measured for both enantiomers of **10** [(+)-**10** at c = 9.6 mM in *n*-hexane and (-)-**10** at c = 12.5 mM] in CCl₄, i.e. at low concentration in the absence of any possible aggregation (see the Supporting Information). Comparison of the experimental and calculated curves (Figure 4) shows conclusive results, which confirm the assignment by VCD. Therefore, the absolute configuration can be unambiguously assigned as (-)-(S)-**10**. Since the asymmetric center is not altered in the subsequent reactions (see Scheme 1), the absolute configuration of all optically active material can be assigned: (-)-(R)-**11**, (+)-(S)-**12**, and (-)-(S)-**13**.



Figure 4. Experimental ORD curves of (+)-10 (c = 9.6 mM in *n*-hexane, triangles, black line) and (-)-10 (c = 12.5 mM in *n*-hexane, diamonds, black line). Calculated ORD values at the B3LYP/6-31G(d) level of theory for (*R*)-10 (squares, gray line) and (*S*)-10 (circles, gray line). The theoretical values were adjusted by scaling down by a factor of 0.3.

Conclusions

We accomplished the synthesis and optical resolution of the asymmetrically silyl-protected trialkynyl(phenyl)methanes (–)-(S)-13 and (+)-(R)-13. The absolute configuration of the precursors (–)-(S)-10 and (+)-(R)-10 was unambiguously determined by using VCD spectroscopy and ORD, in combination with quantum chemical calculations. Future work includes the synthesis of the octaphenyl-EC, which could provide larger quantities of stable material to experimentally study the interesting properties conceived for these cage compounds.^[2,4,13]

Experimental Section

Supporting Information (see footnote on the first page of this article): Experimental procedures, full characterization of all compounds, aggregation studies of compound **10**, and details about calculations.

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