Enantioselective Synthesis and Circular Dichroism of Endocyclic Allenes

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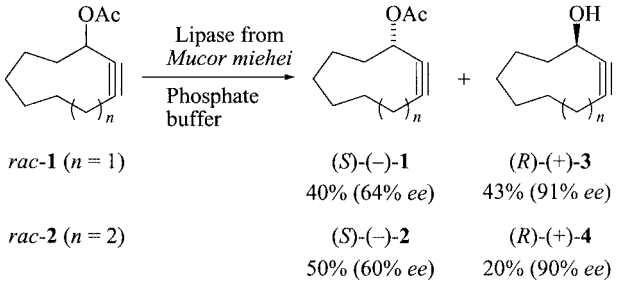
The novel, enantiomerically enriched nine- and ten-membered cyclic allenes (+)-**5a–c** and (–)-**6a–c** were synthesized by lipase-catalyzed kinetic resolution of propargylic acetates **1/2** and subsequent *anti*-stereoselective S_N2'-substitution with magnesium cuprates. The CD spectra of these allenes exhibit distinct features that are a function of the ring size and the alkyl substituent at the allene moiety.

Introduction

The theoretical and experimental investigation of chiroptical properties is an important tool to examine steric and electronic effects in chiral molecules. In the case of axially chiral allenes,[1] studies in the 1980s by Runge et al.[2,3] have led to the development of an empirical chirality function that allows for the calculation of the optical rotation and the theoretical determination of the absolute configuration. The application of more elaborate quantum-chemical methods, for example DFT/MRCI (multi-reference configuration interaction) calculations[4,5] that have been highly useful for the understanding of steric and electronic properties of many classes of chiral molecules, towards allenes is complicated by the existence of many conformers with different circular dichroism. Thus, for a basic theoretical treatment, experimental CD spectra of a series of differently substituted allenes with restricted conformational flexibility are required. Therefore, we decided to synthesize a series of novel, enantiomerically enriched nine- and ten-membered cyclic allenes with various alkyl substituents at the allene moiety.

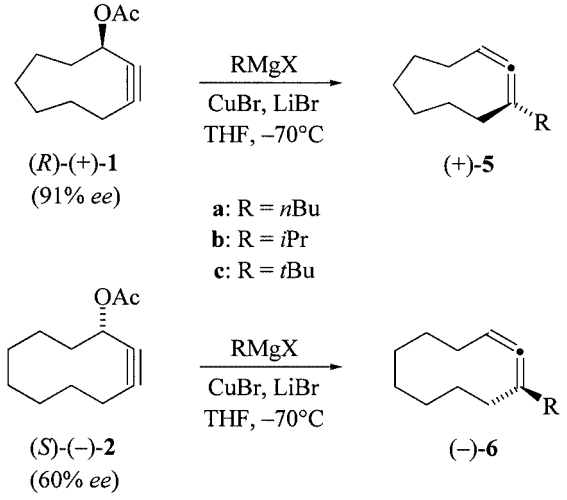
Results and Discussion

Our synthesis started with the known cyclic propargylic acetates **1** and **2**,[6] which were subjected to a lipase-catalyzed kinetic resolution.[7] Among various commercially available enzymes tested, the lipase from *Mucor miehei* gave the best results. Thus, treatment of *rac*-**1** with this enzyme in a phosphate buffer provided (*S*)-(−)-**1** (64% *ee*) and the alcohol (*R*)-(+)-**3**[8] (91% *ee*) in good chemical yield. The corresponding ten-membered substrate *rac*-**3** furnished unchanged acetate (*S*)-(−)-**2** in 50% yield and 60% *ee* besides the alcohol (*R*)-(+)-**4**,[9] which was obtained in 20% yield and 90% *ee*.



Scheme 1. Lipase-catalyzed kinetic resolution of cyclic propargylic acetates **1** and **2**

For the transformation into the desired enantiomerically enriched allenes (*R*)-(+)-**1** [obtained by esterification of



Scheme 2. Synthesis of cyclic allenes (+)-**5** and (−)-**6** by copper-mediated S_N2' substitution

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(*R*)-(+)-**3**] and (*S*)-(−)-**2** were used. The S_N2' substitution reaction of chiral propargylic acetates with organocopper reagents is known to take place with high *anti*-stereoselectivity.[10] Thus, treatment of (*R*)-(+)-**1** with magnesium cuprates obtained from Grignard reagents, copper(I) bromide and lithium bromide,[11] furnished the chiral allenes (+)-**5a**−**c** bearing a *n*-butyl, isopropyl or *tert*-butyl substituent, respectively, with chemical yields ranging from 49 to 80%. The corresponding ten-membered allenes (−)-**6a**−**c** were formed in the analogous reactions of (*S*)-(−)-**2** (50−60% yield). Gas chromatographic analyses of (−)-**6a** and (−)-**6c** using a cyclodextrin derivative as the stationary phase gave a 60% *ee* for both allenes, proving a complete center-to-axis chirality transfer in the S_N2' substitution. Although a chromatographic enantioseparation could not be achieved for the other allenes prepared in this work, it seems safe to assume these were also obtained with 60% *ee* (**6**) and 91% *ee* (**5**), respectively.

The CD spectra of the allenes (+)-**5** and (−)-**6** were recorded in hexane solution and are depicted in Figure 1 and 2. Although the spectra appear very similar at first glance, several differences should be noted. The molar ellipticities are rather different at 180 nm, the *tert*-butyl-substituted allenes give the highest values and the isopropyl-substituted allenes the lowest. Whereas the cyclononadienes **5** exhibit two bands at 220 and 235 nm, only a single positive Cotton effect is displayed by the cyclodecadienes **6**. Due to a lack of literature data, it is not possible at present to discuss these experimental CD spectra in relation to other substituted cyclic allenes; nevertheless, their rather distinct features should provide an impetus for an in-depth theoretical study of the chiroptical properties of cyclic allenes.

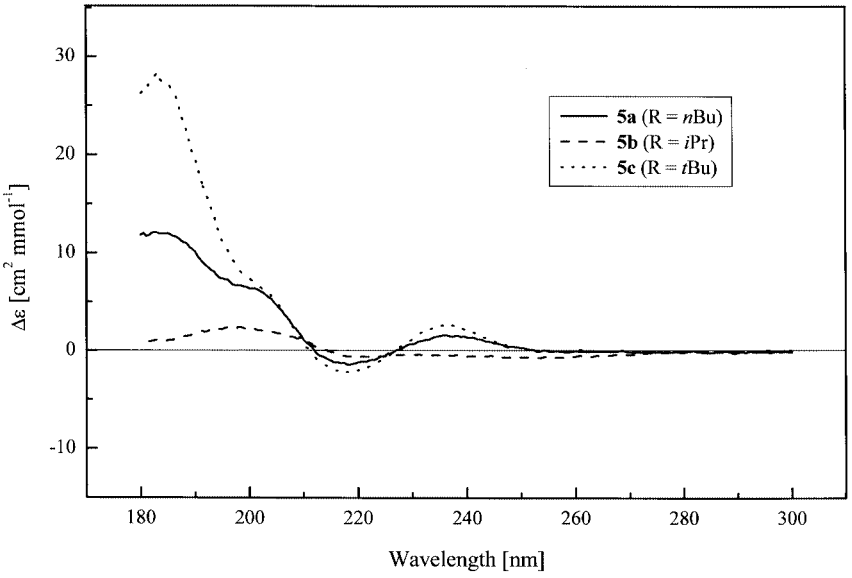

Figure 1. CD spectra of nine-membered allenes (+)-**5a**−**c**

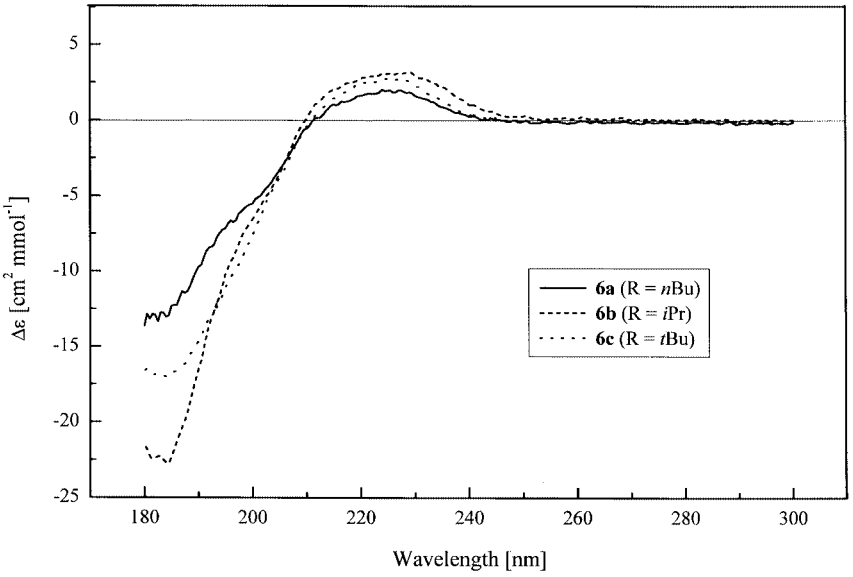

Figure 2. CD spectra of ten-membered allenes (−)-**6a**−**c**

Conclusion

The synthesis of the novel, enantiomerically enriched cyclic allenes (+)-**5** and (−)-**6** was achieved by lipase-catalyzed kinetic resolution of the propargylic acetates **1** and **2**, and subsequent *anti*-stereoselective S_N2' substitution with magnesium cuprates. The CD spectra of these allenes exhibit distinct features that are a function of the ring size and the alkyl substituent at the allene moiety.

Experimental Section

General Remarks: The reactions were performed in oven-dried glassware under Ar. Diethyl ether and THF were distilled from sodium/benzophenone. Lipases were purchased from Fluka. Column chromatography was carried out with Merck silica gel F 60 (70−230 mesh). Enantiomeric ratios were determined by gas chromatography on a Carlo Erba 8000 TOP gas chromatograph with hydrogen as carrier gas and a Lipodex E column. NMR spectra were obtained with a Bruker DRX 400 spectrometer with $CDCl_3$ as solvent and internal standard (^{1}H NMR: δ = 7.26 ppm. ^{13}C NMR: δ = 77.0 ppm). IR spectra were measured with a Bruker IFS 66 spectrometer as a liquid film between NaCl plates. MS and HRMS: Finnigan MAT 8200 (EI, 70 eV). Optical rotations were determined in chloroform solution with a Perkin-Elmer 141 polarimeter in a 10-cm cuvette. CD spectra were obtained in hexane solution with a JASCO J-175 circular dichrograph.

Kinetic Resolution of 3-Acetoxycyclononyne (1): A suspension of *rac*-**1** (500 mg, 2.8 mmol)[6] in phosphate buffer (250 mL, pH = 7.0) was treated with the lipase (372 mg) from *Mucor miehei* (1.3 U/mg). After stirring at room temperature for 41 h, 56% of the starting acetate was consumed, and the mixture was filtered through Celite and washed with diethyl ether. The combined ethereal layers were dried with $MgSO_4$, and the solvent was removed in vacuo. Column chromatography with cyclohexane/ethyl acetate (10:1) furnished (*S*)-(−)-**1**[6] (200 mg, 40% yield, 64% *ee*) and (*R*)-(+)-**3**[6,8] (165 mg, 43% yield, 91% *ee*) as yellow liquids. Optical rotations: (*S*)-(−)-**1** (64% *ee*): $[\alpha]_D^{20}$ = −97.3, *c* = 0.0200 g/mL, $CHCl_3$; (*R*)-(+)-**3** (91% *ee*): $[\alpha]_D^{20}$ = +30.9, *c* = 0.0212 g/mL, $CHCl_3$.

Kinetic Resolution of 3-Acetoxycyclodecyne (2): A suspension of *rac*-**2** (3.11 g, 15.2 mmol)[6] in phosphate buffer (500 mL, pH = 7.0) was treated with the lipase (2.0 g) from *Mucor miehei* (1.3 U/mg). After stirring at room temperature for 5 days, 41% of the starting acetate was consumed, and the reaction was worked up as above. Column chromatography with cyclohexane/ethyl acetate (10:1) furnished (*S*)-(−)-**2**[6] (1.56 g, 50% yield, 60% *ee*) and (*R*)-(+)-**4**[6,9] (0.46 g, 20% yield, 90% *ee*) as yellow liquids. Optical rotations: (*S*)-(−)-**2** (60% *ee*): $[\alpha]_D^{20}$ = −38.4, *c* = 0.0110 g/mL, $CHCl_3$; (*R*)-(+)-**4** (90% *ee*): $[\alpha]_D^{20}$ = +37.1, *c* = 0.0126 g/mL, $CHCl_3$.

(*R*)-(+)-3-Acetoxynonyne (1): A solution of (*R*)-(+)-**3** (247 mg, 1.8 mmol) in CH_2Cl_2 (20 mL) was treated with acetanhydride (350 mg, 3.4 mmol), Et_3N (340 mg, 3.4 mmol), and DMAP (5 mg). After stirring for 10 h at room temperature, the mixture was washed with water and dried with $MgSO_4$. Column chromatography of the crude product with cyclohexane/ethyl acetate (10:1) furnished (*R*)-(+)-**1**[6] (259 mg, 80% yield, 91% *ee*) as a slightly yellow liquid. Optical rotation: (*R*)-(+)-**1** (91% *ee*): $[\alpha]_D^{20}$ = +138.0, *c* = 0.0204 g/mL, $CHCl_3$.

(*R*)-(+)-1-Butylcyclonona-1,2-diene (5a): *n*BuMgBr (4.3 mL, 6.8 mmol, 1.6 M solution in THF) was added slowly to a suspension of CuBr (0.97 g, 6.8 mmol) and LiBr (0.59 g, 6.8 mmol) in THF (40 mL). The mixture was stirred at −70 °C for 1 h , and (*R*)-(+)-**1** (0.41 g, 2.3 mmol, 91% *ee*) in THF (10 mL) was added. After stirring for another 2 h at −70 °C, satd. NH_4Cl solution (10 mL) was added. The mixture was filtered through Celite, the residue was washed with diethyl ether, and the combined organic phases were dried with $MgSO_4$. Column chromatography of the crude product (cyclohexane) afforded (*R*)-(+)-**5a** (300 mg, 74% yield) as a slightly yellow liquid. ^{1}H NMR: δ = 5.38 (m, 1 H), 2.41−2.27 (m, 2 H), 2.05−2.01 (m, 2 H), 1.82−1.40 (m, 14 H), 1.01 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 202.4 (x, C-2), 106.1 (x, C-1), 93.1(+, C-3), 33.2, 32.6, 30.4, 28.8, 28.4, 28.3, 26.4, 25.3, 23.0 (−, C-4, C-5, C-6, C-7, C-8, C-9, C-1′, C-2′, C-3′), 14.2 (+, C-4′) ppm. IR: ṽ = 2925, 2857, 1959, 1459 cm^{-1}. MS: *m*/*z* = 178 (10) [M$^+$], 121 (100), 107 (20), 93 (80), 79 (90), 67 (60), 55 (20). HRMS: *m*/*z*: calcd. for $C_{13}H_{22}$: 178.1721; found 178.1718. Optical rotation: $[\alpha]_D^{20}$ = +80.3, *c* = 0.0112 g/mL, $CHCl_3$.

(*S*)-(+)-1-(1-Methylethyl)cyclonona-1,2-diene (5b): Analogous to the synthesis of **5a**, CuBr (0.97 g, 6.8 mmol), LiBr (0.59 g, 6.8 mmol) in THF (40 mL), *i*PrMgCl (3.4 mL, 6.8 mmol, 2.0 M solution in THF), and (*R*)-(+)-**1** (0.41 g, 2.3 mmol, 91% *ee*) in THF (10 mL) afforded (*S*)-(+)-**5b** (300 mg, 80% yield) as a slightly yellow liquid. ^{1}H NMR: δ = 5.41 (m, 1 H), 2.40−2.26 (m, 2 H), 2.17−2.15 [sept, *J* = 7.5 Hz, 1 H, C*H*(CH$_3$)$_2$], 1.76−1.65 (m, 10 H), 1.21 [d, *J* = 7.5 Hz, 6 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR: δ = 201.7 (x, C-2), 113.0 (x, C-1), 94.5 (+, C-3), 32.4 (+, C-1′), 31.3, 29.2, 28.9, 28.3, 26.5, 26.2 (−, C-4, C-5, C-6, C-7, C-8, C-9), 22.5, 21.9 (+, C-2′) ppm. IR: ṽ = 2959, 2925, 2860, 1954, 1361 cm^{-1}. MS: *m*/*z* = 164 (10) [M$^+$], 148 (10), 133 (8), 121 (40), 107 (8), 93 (77), 79 (100), 67 (20), 57 (30). HRMS: *m*/*z*: calcd. for $C_{12}H_{20}$: 164.1565; found 164.1568. Optical rotation: $[\alpha]_D^{20}$ = +43.5, *c* = 0.0115 g/mL, $CHCl_3$.

(*S*)-(+)-1-(1,1-Dimethylethyl)cyclonona-1,2-diene (5c): Analogous to the synthesis of **5a**, CuBr(0.97 g, 6.8 mmol), LiBr (0.59 g, 6.8 mmol) in THF (40 mL), *t*BuMgCl (3.4 mL, 6.8 mmol, 2.0 M solution in THF), and (*R*)-(+)-**1** (0.41 g, 2.3 mmol, 91% *ee*) in THF (10 mL) afforded (*S*)-(+)-**5c** (200 mg, 49% yield) as a slightly yellow liquid. ^{1}H NMR: δ = 5.32 (m, 1 H), 2.32−2.24 (m, 2 H), 1.87−1.55 (m, 8 H), 1.45−1.38 (m, 2 H), 1.19 [s, 9 H, C(C*H*$_3$)$_3$] ppm. ^{13}C NMR: δ = 201.1 (x, C-2), 114.7 (x, C-1), 93.7 (+, C-3), 33.5 [x, *C*(CH$_3$)$_3$], 29.3 [+, C(*C*H$_3$)$_3$], 29.1, 28.5, 27.7, 27.1, 26.3, 26.1 (−, C-4, C-5, C-6, C-7, C-8, C-9) ppm. IR: ṽ = 2936, 2961, 2861, 1954, 1454, 1326 cm^{-1}. MS: *m*/*z* = 179 (1) [M + 1]$^+$, 147 (20), 121 (30), 107 (18), 93 (80), 79 (100), 67 (40), 57 (50). HRMS: *m*/*z*: calcd. for $C_{13}H_{22}$: 178.1721; found 178.1722. Optical rotation: $[\alpha]_D^{20}$ = +73.9, *c* = 0.0124 g/mL, $CHCl_3$.

(*S*)-(−)-1-Butylcyclodeca-1,2-diene (6a): Analogous to the synthesis of **5a**, CuBr (0.60 g, 4.2 mmol), LiBr (0.36 g, 4.2 mmol) in THF (30 mL), *n*BuMgBr (2.6 mL, 4.2 mmol, 1.6 M solution in THF), and (*S*)-(−)-**2** (0.27 g, 1.3 mmol, 60% *ee*) in THF (10 mL) afforded (*S*)-(−)-**6a** (128 mg, 50% yield, 60% *ee*) as a slightly yellow liquid. ^{1}H NMR: δ = 5.23 (m, 1 H), 2.41−2.29 (m, 2 H), 2.07−1.84 (m, 4 H), 1.69−1.47 (m, 14 H), 1.01 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 201.9 (x, C-2), 104.5 (x, C-1), 91.8 (+, C-3), 32.3, 31.9, 30.3, 28.4, 26.3, 25.9, 24.6, 23.3, 22.9, 22.5 (−, C-4, C-5, C-6, C-7, C-8, C-9, C-10, C-1′, C-2′, C-3′), 14.2 (+, C-4′) ppm. IR: ṽ = 2924, 2857, 1959, 1459 cm^{-1}. MS: *m*/*z* = 192 (1) [M$^+$], 135 (30), 107 (40), 93 (25), 79 (100), 65 (25). HRMS: *m*/*z*: calcd. for $C_{14}H_{24}$: 192.1878; found 192.1886. Optical rotation: $[\alpha]_D^{20}$ = −48.6, *c* = 0.0121 g/mL, $CHCl_3$.

(*R*)-(−)-1-(1-Methylethyl)cyclodeca-1,2-diene (6b): Analogous to the synthesis of **5a**, CuBr (0.60 g, 4.2 mmol), LiBr (0.36 g, 4.2 mmol) inTHF (30 mL), *i*PrMgCl (2.1 mL, 4.2 mmol, 2.0 M solution in THF), and (*S*)-(−)-**2** (0.27 g, 1.3 mmol, 60% *ee*) in THF (10 mL) afforded (*R*)-(−)-**6b** (142 mg, 60% yield) as a slightly yellow liquid. ^{1}H NMR: δ = 5.26 (m, 1 H), 2.40−2.28 (m, 2 H), 2.14−2.07 [m, 1 H, C*H*(CH$_3$)$_2$], 1.98−1.87 (m, 2 H), 1.68−1.53 (m, 10 H), 1.17 [d, *J* = 7.5 Hz, 6 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR: δ = 200.9 (x, C-2), 111.0 (x, C-1), 92.9 (+, C-3), 30.9 (+, C-1′), 30.1, 28.5, 26.1, 25.9, 24.8, 23.2, 22.5 (−, C-4, C-5, C-6, C-7, C-8, C-9, C-10), 22.2, 21.8 (+, C-2′) ppm. IR: ṽ = 2958, 2926, 2863, 1956, 1459 cm^{-1}. MS: *m*/*z* = 178 (2) [M$^+$], 135 (30), 107 (45), 91 (100), 79 (90), 65 (35). HRMS: *m*/*z*: calcd. for $C_{13}H_{22}$: 178.1721; found 178.1725. Optical rotation: $[\alpha]_D^{20}$ = −40.0, *c* = 0.0096 g/mL, $CHCl_3$.

(*R*)-(−)-1-(1,1-Dimethylethyl)cyclodeca-1,2-diene (6c): Analogous to the synthesis of **5a**, CuBr (0.60 g, 4.2 mmol), LiBr (0.36 g, 4.2 mmol) in THF (30 mL), *t*BuMgCl (2.1 mL, 4.2 mmol, 2.0 M solution in THF), and (*S*)-(−)-**2** (0.27 g, 1.3 mmol, 60% *ee*) in THF (10 mL) afforded (*S*)-(−)-**6c** (131 mg, 51% yield, 60% *ee*) as a slightly yellow liquid. ^{1}H NMR: δ = 5.24−5.19 (m, 1 H), 2.34−2.23 (m, 2 H), 1.80−1.72 (m, 2 H), 1.54−1.48 (m, 2 H), 1.31−1.28 (m, 8 H), 0.96 [s, 9 H, C(C*H*$_3$)$_3$] ppm. ^{13}C NMR: δ = 200.9 (x, C-2), 113.6 (x, C-1), 92.8 (+, C-3), 33.5 [x, *C*(CH$_3$)$_3$], 29.6 [+, C(*C*H$_3$)$_3$], 28.6, 26.9, 26.5, 25.6, 24.9, 24.0, 22.6 (−, C-4, C-5, C-6, C-7, C-8, C-9, C-10) ppm. IR: ṽ = 2961, 2862, 1952, 1461, 1324 cm^{-1}. MS: *m*/*z* = 192 (1) [M$^+$], 135 (30), 107 (40), 93 (25), 79 (100), 65 (25). HRMS: *m*/*z*: calcd. for $C_{14}H_{24}$: 192.1878; found 192.1879. Optical rotation: $[\alpha]_D^{20}$ = −34.2, *c* = 0.0104 g/mL, $CHCl_3$.

Acknowledgments

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