JOC*Note*

Synthesis of Optically Active 5-Alkoxy-6-methylcyclohex-2-en-1-ones and 4-Alkoxy-5-methylcyclopent-1-enyl Benzoate

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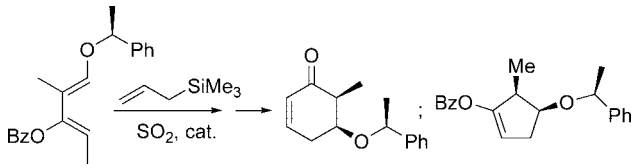
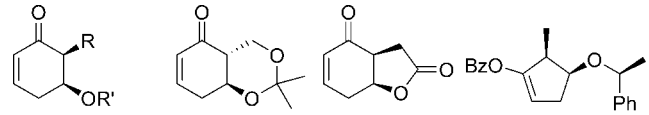
Received September 20, 2008



The reaction of (−)-(1*E*,3*Z*)-2-methyl-1-((1*S*)-1-phenylethoxy)penta-1,3-dien-3-ol benzoate with allyltrimethylsilane in SO_2 and in the presence of a catalytic amount of Tf_2NTMS gives a silyl sulfinate intermediate that furnishes (−)-(6*Z*,1′*S*,4*S*,5*S*)-5-methyl-4-(1′-phenylethoxy)octa-1,6-dien-6-yl benzoate after acidic workup. The latter undergoes ring-closing metathesis producing (−)-(2*S*,3*S*)-2-methyl-3-((1*S*)-1-phenylethoxy)cyclopent-5-en-1-yl benzoate. It has been converted also into the corresponding trimethylsilyl enol ether. After oxidation, an enone is obtained that undergoes ring-closing metathesis giving (−)-(5*S*,6*S*)-6-methyl-5-((1*S*)-1-phenylethoxy)cyclohex-2-en-1-one.

Enantiomerically enriched cyclohex-2-enone derivatives are extremely useful building blocks for the preparation of biologically active compounds, including natural products.[1−8] Among the various types of cyclohex-2-enone derivatives, 5-hydroxy- and 5-alkoxycyclohex-2-enones represent the most attractive and versatile chiral building blocks,[9−15] and several approaches for their synthesis have been proposed.[16,17] The two 5-siloxycyclohex-2-enones **1** and **2**[18] and bicyclic compounds **3**[19] and **4**[20] are the only enantiomerically enriched 6-alkyl-substituted 5-hydroxycyclohex-2-enone derivatives reported thus far.



1 R = Me, R' = TBS **3** **4** **6**
2 R = CH_2Ph, R' = TBS
5 R = Me, R' = (1*S*)-1-phenylethyl

The synthesis of 5-hydroxy-, 5-alkoxy-, and 5-siloxycyclohex-2-enones is a challenge because these compounds are prone to β-eliminations generating the corresponding phenols, under basic or acidic conditions. We present here an original approach to the synthesis of enantiomerically enriched 6-alkyl-5-alkoxycyclohex-2-enones. The method is illustrated for the preparation of derivative **5**. We disclose also the synthesis of the enantiomerically enriched cyclopentanone enol benzoate **6**, a yet unknown compound. Apart from their potential as synthetic intermediates, both **5** and **6** are of interest for the perfume industry.[21−32]

In 2004, we reported that the reactions of 1-alkoxy-1,3-dien-3-ol esters (**7**) with sulfur dioxide and allylsilanes (**10**) generate enol esters of type **13** with high stereoselectivity. The reactions imply equilibrium of dienes **7** + SO_2 with corresponding

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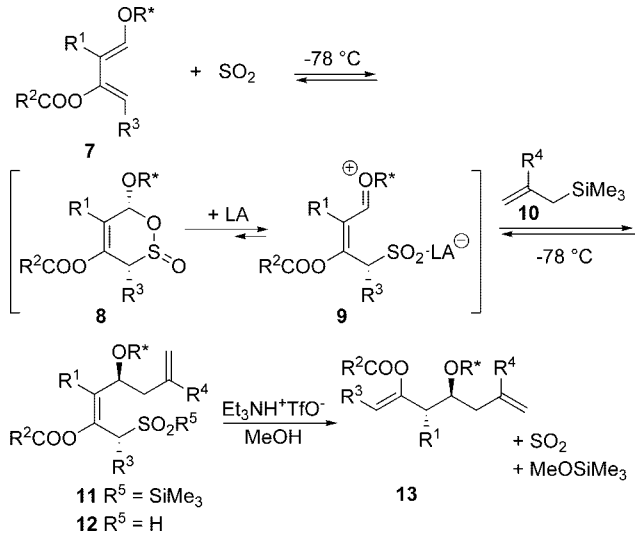
10.1021/jo801981c CCC: $40.75 © 2009 American Chemical Society
Published on Web 11/14/2008

SCHEME 1

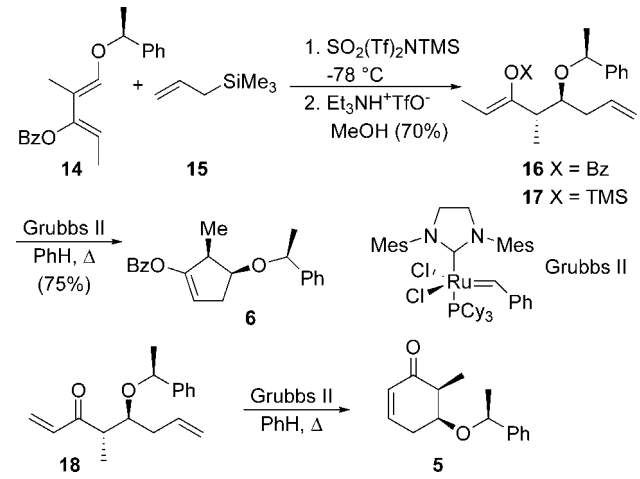


unstable sultines **8** that, in the presence of a protic or Lewis acid catalyst, are isomerized into zwitterionic species **9** that are allylated by the allylsilanes **10** producing silyl sulfinates **11**. After acidic workup, the corresponding β,γ-unsaturated sulfinic acids **12** undergo stereoselective retro-ene eliminations of SO_2 with formation of **13** (Scheme 1).[33]

In this process, sulfur dioxide permits the Umpolung of the electron-rich dienes **7** generating oxyallyl cationic intermediates (**9**) that are quenched by electron-rich alkenes such as allylsilanes.[34,35] Compounds **13** undergo ring-closing metathesis[36−38] catalyzed by the second-generation Grubbs' catalyst.[39−42] An example is given with enol benzoate **16** (ee 97%) obtained by reaction of (−)-(1*E*,3*Z*)-2-methyl-1-((1*S*)-1-phenylethoxy)-penta-1,3-dien-3-ol benzoate (**14**, ee 97%) with SO_2 and allyltrimethylsilane (**15**) in the presence of a catalytic amount of $(CF_3SO_2)_2NSiMe_3$ at −78 °C.[43] Thus, in the presence of 0.1 equiv of Grubbs' II catalyst (dry benzene, 80 °C, 30 min), cyclopentenyl benzoate **6** was obtained in 75% yield. To our knowledge, this is the first example of ring-closing metathesis involving an enol ester and an alkene (Scheme 2), although several examples of ring-closing alkene metatheses involving enol ethers or enoxysilanes with alkenes have been presented.[44,45]

Enol benzoate **16** was converted into its silyl enol ether **17** by reaction with MeLi·LiBr in Et_2O at −78 °C to generate the corresponding ethyl ketone that was not purified but used directly in the silylation step with Me_3SiOTf/Et_3N. Enoxysilane

SCHEME 2



17 was obtained in 82% yield (based on **16**) and was then submitted to oxidation with an excess of 2-iodoxybenzoic acid (IBX) and 4-methoxypyridine *N*-oxide (MPO) in DMSO (25 °C, 16 h)[46,47] to produce enone **18** in 64% yield. In the presence of 10 mol % of Grubbs' II catalyst in dry benzene (80 °C, 30 min), ring-closing alkene metathesis furnished cyclohexenone **5** in 85% yield. Because of the neutral conditions used for the latter reaction, heating of **5** did not induce β-elimination of 1-phenylethanol.

We believe that the chemistry disclosed here can be applied to the synthesis to further enantiomerically enriched 5-alkoxy-6-alkylcyclohex-2-enone derivatives starting from dienes of type **7** ($R^1 \neq$ Me). As both enantiomeric forms of the chiral auxiliary (1-phenylethanol) are commercially available, the cyclohexenones can be obtained in both their enantiomeric forms.

Experimental Section

Preparation of (−)-(2*S*,3*S*)-2-Methyl-3-((1*S*)-1-phenylethoxy)-cyclopent-5-en-1-yl Benzoate (6). To a solution of Grubbs' second-generation catalyst (31 mg, 0.036 mmol, 0.1 equiv) in dry benzene (70 mL) under argon atmosphere was added a solution of **16** (0.133 g, 0.36 mmol, 1 equiv).[43] The resulting solution was heated under reflux for 0.5 h. Solvent was evaporated in vacuo and the residue purified by FC (PE/EtOAc = 95:5): 88 mg (75%), colorless oil; $[\alpha]^{25}_D = -176$ (c = 1.40, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 400 MHz) 8.07 (d, 2H, J = 8.0 Hz), 7.60 (t, 1H, J = 7.0), 7.47 (t, 2H, J = 7.7), 7.36−7.25 (m, 5H), 5.44 (ddd, 1H, J = 2.5, 2, 1.1), 4.46 (q, 1H, J = 6.4), 4.13 (dt, 1H, J = 7.4, 6.8), 3.00 (dqt, 1H, J = 7.4, 6.8, 1.5), 2.42 (ddd, 1H, J = 16.0, 7.4, 3.2), 2.34 (dddd, 1H, J = 16.0, 6.8, 2.5), 1.43 (d, 3H, J = 6.4), 1.18 (d, 3H, J = 7.0); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) 164.2, 152.8, 144.5, 133.4, 129.8, 128.6, 128.4, 127.4, 126.4, 126.3, 109.3, 76.9, 76.1, 40.5, 34.4, 24.0, 11.2; MALDI-HRMS calcd. for $C_{21}H_{22}O_3Na^+$ 345.1467, found 345.1480.

(+)-(4*S*,5*S*)-4-Methyl-5-((1*S*)-1-phenylethoxy)octa-1,7-dien-3-one (18). A solution of **16** (3.32 g, 9.1 mmol, 1 equiv) in Et_2O (50 mL) was added at −78 °C to a solution of MeLi·LiBr (2.2 M, 10.3 mL, 22.7 mmol, 2.5 equiv) in Et_2O (24 mL). The reaction mixture was stirred at −78 °C overnight and afterward poured slowly into a saturated aqueous solution of NH_4Cl (200 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL), washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The resulting ethyl

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ketone (2.23 g, ~94%) was dried under reduced pressure (0.06 Torr, 12 h) and used without further purification. To a solution of the ethyl ketone (2.23 g, 8.56 mmol, 1 equiv) in CH_2Cl_2 (40 mL) at −20 °C was added NEt_3 (3.58 mL, 25.7 mmol, 3 equiv) followed by $Me_3SiOSO_2CF_3$ (2.01 mL, 11.1 mmol, 1.3 equiv). The reaction mixture was allowed to reach 20 °C in 2 h. Cold pentane (300 mL (−50 °C)) was added, and the resulting suspension was filtered through a small pad of silica gel (suspended in pentane containing 2% of NEt_3). The organic phase was sequentially washed with 15% aqueous solution of citric acid (3 × 70 mL), saturated aqueous solution of $NaHCO_3$ (3 × 50 mL), and brine (2 × 50 mL), dried (Na_2SO_4), and evaporated in vacuo. The resulting oil (**17**) was dried under reduced pressure (0.06 Torr, 12 h): yield 2.49 g (82% over two steps from **16**), colorless oil. Analytical data for (2*S*,3*S*)-(1-ethylidene-2-methyl-3-((1*S*)-1-phenylethoxy)hex-5-enyloxy)trimethylsilane (**17**): ^{1}H NMR ($CDCl_3$, 400 MHz) 7.36−7.25 (m, 5H), 5.65 (ddt, 1H, J = 17.3, 10.2, 7.0), 4.96 (dm, 1H, J = 17.3), 4.92 (dm, 1H, J = 10.2), 4.62 (q, 1H, J = 6.4), 4.52 (q, 1H, J = 6.4), 3.53 (dt, 1H, J = 7.0, 3.8), 2.52 (dq, 1H, J = 7.0, J = 6.4), 2.18−2.03 (m, 2H), 1.53 (dd, 3H, ^3J = 7.0, 1.3), 1.42 (d, 3H, J = 6.4), 1.02 (d, 3H, J = 7.0), 0.19 (s, 9H). To a solution of IBX (0.252 g, 0.90 mmol, 3 equiv) in DMSO (1.0 mL) was added MPO·H_2O (0.112 g, 0.90 mmol, 3 equiv) at 25 °C. The resulting mixture was allowed to stay for 30 min. Then a solution of **17** (0.10 g, 0.30 mmol, 1 equiv) in DMSO (0.5 mL) was added, and the resulting mixture was stirred at 25 °C for 16 h. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added, and the product was isolated by extraction with Et_2O (3 × 7 mL). The collected organic layers were washed with brine (3 × 6 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was purified by FC (PE/EtOAc = 95:5) yielding 50 mg (64% from **17**): colorless oil; $[\alpha]^{25}_D$ = +73 (c = 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35−7.24 (m, 5H), 6.44 (dd, 1H, J = 17.2, 10.5), 6.25 (dd, 1H, J = 17.2, 1.2), 5.78 (dd, 1H, J = 10.5, 1.2), 5.74 (ddt, 1H, J = 17.2, 10.4, 7.4), 4.99 (dm, 1H, J = 10.4), 4.96 (dm, 1H, J = 17.2), 4.43 (q, 1H, J = 6.2), 3.72 (dt, 1H, J = 8.0, 4.9), 3.21 (dq, 1H, J = 8.0, 6.8), 2.13 - 2.06 (m, 2H), 1.32 (d, 3H, J = 6.2), 1.03 (d, 3H, J = 6.8); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 203.5, 144.2, 136.5, 134.1, 128.3, 128.1, 127.5, 126.6, 117.3, 78.5, 46.2, 35.5, 23.6, 12.2; ESI-HRMS calcd for $[C_{17}H_{22}O_2 + H]^+$ 259.1698, found 259.1692.

(−)-(5*S*,6*S*)-6-Methyl-5-((1*S*)-1-phenylethoxy)cyclohex-2-en-1-one (5). To a solution of Grubb's second-generation catalyst (98 mg, 0.116 mmol, 0.1 equiv) in dry benzene (240 mL) under argon atmosphere was added a solution of **18** (0.30 g, 1.16 mmol, 1 equiv). The resulting solution was heated under reflux for 0.5 h. Solvent was evaporated in vacuo, and the residue was purified by FC (PE/EtOAc = 9:1): yield 0.227 mg (85%); colorless oil; $[\alpha]^{25}_D$ = −130 (c = 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.37−7.25 (m, 5H), 6.69 (dt, 1H, J = 10.2, 3.8), 6.25 (dt, 1H, J = 10.2, 1.9), 4.49 (q, 1H, J = 7.0), 3.85 (dt, 1H, J = 7.0, 4.5), 2.76 (dq, 1H, J = 7.0, 3.8), 2.39 (dddd, 1H, J = 19.0, 6.0, 3.2, 1.9), 2.34 (dddd, 1H, J = 19.0, 5.1, 1.9, 1.9), 1.42 (d, 3H, J = 6.4), 1.23 (d, 3H, J = 7.0); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 198.1, 146.1, 144.1, 129.1, 128.5, 127.6, 126.2, 76.4, 75.1, 45.9, 30.0, 24.5, 10.5; MALDI-HRMS calcd for $C_{15}H_{18}O_2Na^+$ 253.1204, found 253.1209.

Acknowledgment. We are grateful to the Swiss National Science Foundation for financial support and to Mr. M. Rey, F. Sepulveda, Dr. S. R. Dubbaka, Ms. C. Exner, and Mr. S. Laclef for their technical help.

Supporting Information Available: Analytical details for products **6**, **5**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801981C