Application of the Silyloxy Cope Rearrangement of Chiral Aldol Products Towards a Synthesis of (+)-Lasiol

Christoph Schneider

Institut für Organische Chemie der Georg-August-Universität Göttingen,
Tammannstraße 2, D-37077 Göttingen, Germany
Fax: (internat) + 49(0)551/399660
E-mail: cschnei1@gwdg.de

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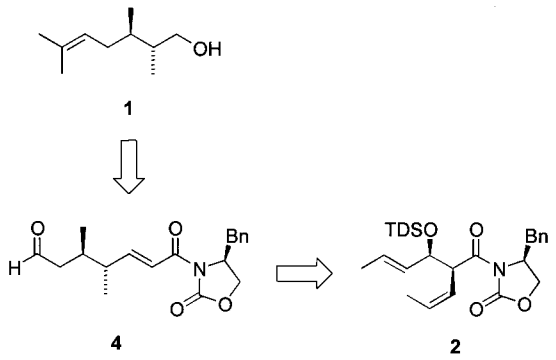
A stereoselective total synthesis of the natural product (+)-lasiol (**1**) has been achieved. The key step of our synthesis is a silyloxy-Cope rearrangement of the chiral, silylated aldol product **2** which proceeds selectively through the chair-like transition state with the silyloxy group in the pseudoaxial and the carboximide group in the pseudoequatorial position. The two methyl-substituted stereogenic centers of the natural product are generated with ds > 97:3. The rearrangement product **4** is converted to the natural product via a Wittig olefination reaction and an oxidative cleavage of a double bond, respectively.

The acyclic monoterpenol (+)-lasiol (**1**) was isolated in 1990 by Jones as the major volatile component of the mandibular gland secretion of the male ant *Lasius meridionalis*.[1] Despite the apparently simple structure the two adjacent stereogenic centers of lasiol at unfunctionalized carbon atoms present a problem for stereoselective synthesis. Thus, only one synthesis of (+)-lasiol (**1**) has been achieved to date starting from methyl (*S*)-3-hydroxy-2-methylpropionate which is available from isobutyric acid by enzymatic oxidation.[2] This approach clearly takes advantage of the methyl-bearing chiral center in the starting material and only needs to generate the other one diastereoselectively.

We wish to report a straightforward and stereoselective synthesis of (+)-lasiol (**1**) which is based on the silyloxy-Cope rearrangement of the chiral aldol product **2** (TDS = thexyldimethylsilyl). As the retrosynthetic analysis reveals both stereogenic centers of the natural product were intended to originate in the sigmatropic rearrangement (Scheme 1). Previous reports from this laboratory have established that 1,5-dienes with a *syn*-aldol substitution pattern − OTDS at C-3 and COX_c at C-4 − undergo rapid and highly stereoselective thermal Cope rearrangements.[3][4] The multifunctional products thus formed have been converted into enantiopure and polyalkylated tetrahydropyrans[5] and piperidines[6] as well as substructures of polyol natural products.[7]

Our synthesis started with the chiral, silylated *syn*-aldol product **2** which is easily available via the Evans asymmetric aldol methodology[8] in 72% overall yield as we have described previously.[3b] The Cope rearrangement of **2** proceeded cleanly at 180°C with > 97:3 diastereoselectivity to afford the silyl enol ether **3** which was desilylated through the addition of *p*-TsOH to the reaction mixture to furnish the aldehyde **4** as a single stereoisomer in 63% yield (Scheme 2). Inspection of the two competing chairlike transition structures **A** and **B** reveals that the rearrangement selectively proceeds through **A** which has the lean silyloxy group in the pseudoaxial and the large carboximide group in the pseudoequatorial position. In addition, transition state **B** suffers from a severe 1,3-diaxial interaction between the carboximide and one of the methyl groups at the diene which destabilizes transition state **B** relative to **A**. The characteristic coupling constants of J = 15.5 Hz for the (2′*E*)-double bond and J = 6.0 Hz for the (6′*Z*)-silyl enol ether double bond in **3** support this assumption. The stereochemical assignment of the newly formed chiral centers was made by the conversion of **3** into the natural product and is in agreement with a crystal structure analysis of a related product.[5]

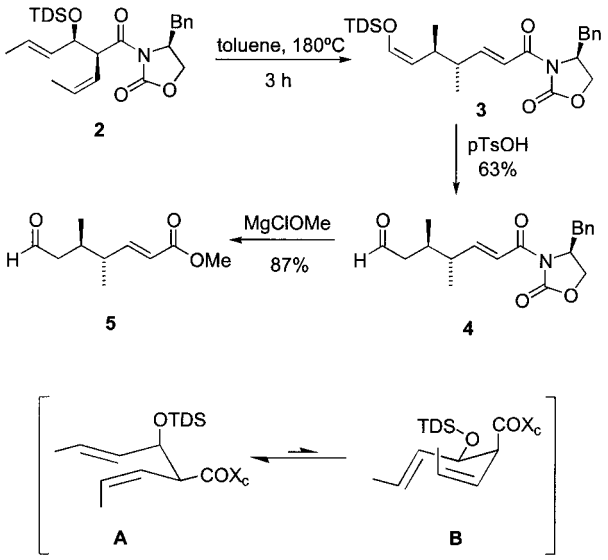
Scheme 1



The aldehyde **4** already has both stereogenic centers of (+)-lasiol properly in place with the correct absolute configuration. Moreover, the aldehyde moiety on one end of the molecule and the double bond on the other end can now be advantageously used to elaborate the natural product via Wittig olefination and oxidative cleavage, respectively. Attempted Wittig reaction of **4**, however, gave only

  1434−193X/98/0808−1661 $ 17.50+.50/0

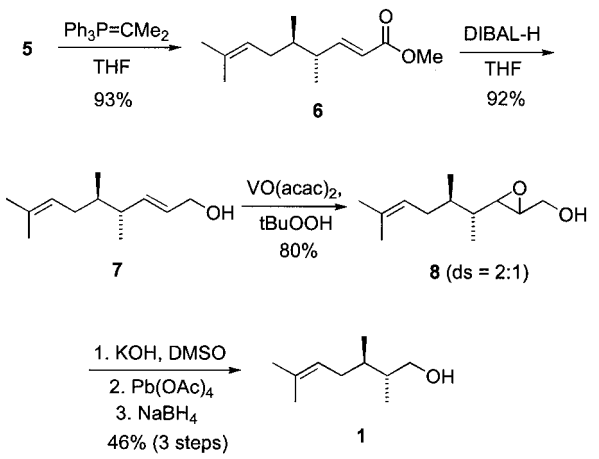
Scheme 2



low yields of the desired product presumably because the Wittig reagent attacks the highly reactive α,β-unsaturated imide in a cyclopropanation reaction.[9] In order to attenuate the reactivity the α,β-unsaturated imide **4** was transformed to the methyl enoate **5** in 87% yield.[10]

Wittig reaction of **5** with isopropylidene triphenyl phosphorane furnished the olefinated ester **6** in excellent yield (Scheme 3). In order to differentiate the two double bonds the enoate **6** was reduced with iBu$_2$AlH to the allylic alcohol **7**. A chemoselective epoxidation using the Sharpless protocol [VO(acac)$_2$, tBuOOH][11] gave rise to the 2,3-epoxy alcohol **8** which was obtained as a 2:1 stereoisomeric mixture. No effort was made to determine the stereochemistry of the major stereoisomer. In spite of the precedent in the literature[12] we were not able to cleave the epoxide **8** in one step with periodic acid. Therefore, base-catalyzed hydrolysis of the epoxide gave a mixture of two triols in quantitative yield. Oxidative cleavage of the triols with Pb(OAc)$_4$ furnished the corresponding aldehyde which was immediately reduced with NaBH$_4$ to give synthetic (+)-lasiol (**1**) which was identical with the published spectroscopic data of the natural product.[1][2]

Scheme 3



In conclusion, a stereoselective synthesis of (+)-lasiol (**1**) has been achieved with the silyloxy-Cope rearrangement of the chiral aldol product **2** as the key step. The sigmatropic rearrangement not only gives easy access to both chiral centers of (+)-lasiol with complete chirality transfer but also provides the functional groups necessary for a straightforward conversion of the rearrangement product into the natural product.

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Experimental Section

General: All reactions requiring anhydrous conditions were performed in flame-dried flasks under nitrogen. The aqueous workup was routinely carried out by adding a saturated sodium bicarbonate solution to the reaction mixture, extracting the aqueous layer repeatedly with diethyl ether and drying the combined organic phases over magnesium sulfate. Tetrahydrofuran was freshly distilled from LiAlH$_4$, toluene from sodium, dichloromethane, triethylamine and 2,6-lutidine from CaH$_2$. Dibutylboryl trifluoromethanesulfonate was purchased as 1 M solution in CH$_2$Cl$_2$ from Aldrich. Products were purified by flash chromatography on silica gel 230−400 mesh with various mixtures of diethyl ether (E) and petroleum ether (PE). − Optical rotation: Perkin-Elmer 241. − NMR: Varian VXR-200, VXR-500 and Bruker AM-300. − IR: Bruker IFS 25 FT-IR. − MS: Finnigan MAT 95A spectrometer.

(2′E,4S,4′R,5′R)-4-Benzyl-3-[4′,5′-dimethyl-7′-oxo-2′-heptenoyl]oxazolidin-2-one (**4**): 1.50 g (3.18 mmol) of the chiral, silylated aldol product **2** were dissolved in 25 ml toluene and heated at 180°C for 3 h. 1.00 g (5.26 mmol) of *p*-TsOH-H$_2$O was added to the reaction mixture at room temperature and stirred for 15 min to effect hydrolysis of the silyl enol ether. After aqueous workup and removal of solvents flash chromatography (E/PE 1:2) afforded 655 mg (63%) of the title compound as a colorless oil. − $[\alpha]_D^{20}$ = +21.5 (c = 1, CHCl$_3$). − ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.99 (d, J = 6.5 Hz, 3 H, CH$_3$), 1.12 (d, J = 6.5 Hz, 3 H, CH$_3$), 2.15−2.65 (m, 4 H, 4′-H, 5′-H, 6′-H$_2$), 2.80 (dd, J = 13.0, 9.5 Hz, 1 H, benzyl-H), 3.37 (dd, J = 13.0, 3.0 Hz, 1 H, benzyl-H), 4.18−4.30 (m, 2 H, 5-H$_2$), 4.72 (mc, 1 H, 4-H), 7.07 (dd, J = 15.5, 7.0 Hz, 1 H, 3′-H), 7.10−7.35 (m, 6 H, 2′-H, phenyl-H), 9.78 (br s, 1 H, 7′-H). − ^{13}C NMR (50 MHz, CDCl$_3$): δ = 16.36, 16.86, 32.37, 37.89, 41.35, 48.26, 55.34, 66.18, 120.7, 127.3, 128.9, 129.4, 135.3, 153.4 (2 C), 164.8, 201.9. − IR (film): ν = 1780, 1722, 1682, 1632 cm^{-1}. − EI-MS; *m/z* (%): 329 (9) [M$^+$], 259 (16) [retro-Cope + retro-aldol product], 230 (86), 153 (100) [M$^+$ − oxazolidinone]. − C$_{19}$H$_{23}$NO$_4$ (329.4): calcd. C 69.28, H 7.04; found C 69.07, H 7.09.

Methyl (2E,4R,5R)-4,5-Dimethyl-7-oxo-2-heptenoate (**5**): 0.65 ml (1.95 mmol) MeMgCl (3 M in diethyl ether) were added to 5 ml methanol at 0°C and stirred for 5 min. In a second flask 540 mg (1.64 mmol) of **4** were dissolved in 10 ml CH$_2$Cl$_2$ and 10 ml methanol and treated with the Mg methoxide solution at 0°C for 5 min. After aqueous workup and removal of solvents column chromatography (E/PE 1:3) of the crude product gave 262 mg (87%) of methyl ester **5** as a colorless oil. − $[\alpha]_D^{20}$ = −51.0 (c = 1, CHCl$_3$). − ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.96 (d, J = 6.5 Hz, 3 H, CH$_3$), 1.07 (d, J = 6.5 Hz, 3 H, CH$_3$), 2.12−2.55 (m, 4 H, 4-H, 5-H, 6-H$_2$), 3.75 (s, 3 H, CO$_2$Me), 5.82 (d, J = 15.0 Hz, 1 H, 2-H), 6.88 (dd, J = 15.0, 7.5 Hz, 1 H, 3-H), 9.76 (br s, 1 H, 7-H). − ^{13}C

NMR (50 MHz, $CDCl_3$): δ = 16.40, 16.68, 32.31, 40.89, 48.30, 51.51, 121.2, 151.4, 166.8, 202.0. − IR (film): ν = 1724, 1656 cm^{-1}. − EI-MS; *m/z* (%): 184 (1) [M^+], 125 (38) [$M^+ - CO_2Me$], 114 (100) [retro-Cope + retro aldol product]. − $C_{10}H_{16}O_3$ (184.2): calcd. C 65.19, H 8.75; found C 65.29, H 8.73.

Methyl (2E,4R,5R)-4,5,8-Trimethyl-2,7-nonadienoate (**6**): 540 mg (1.25 mmol) isopropyl triphenylphosphonium iodide were suspended in 10 ml THF and treated with 0.52 ml (1.30 mmol) *n*-butyllithium (2.5 M in hexane) at 0°C for 15 min. The deep red solution was cooled to −78°C and a solution of 210 mg (1.14 mmol) of aldehyde **5** in 5 ml THF was added dropwise. The reaction mixture was warmed to 0°C within 30 min and stirred for another 30 min at 0°C. After aqueous workup and removal of solvents column chromatography (E/PE 1:5) gave 222 mg (93%) of the title compound as a colorless oil. − $[\alpha]_D^{20}$ = −56.0 (*c* = 1.7, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.06 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.46−2.00 (m, 3 H), 1.59 (s, 3 H, allylic-CH_3), 1.71 (s, 3 H, allylic-CH_3), 2.31 (mc, 1 H), 3.73 (s, 3 H, CO_2Me), 5.08 (mc, 1 H, 7-H), 5.78 (dd, *J* = 15.0, 1.0 Hz, 1 H, 2-H), 6.93 (dd, *J* = 15.0, 8.0 Hz, 1 H, 3-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.08, 16.94, 17.90, 25.84, 32.76, 38.67, 40.68, 51.36, 120.3, 122.9, 132.4, 153.0, 167.2. − IR (film): ν = 1728, 1656 cm^{-1}. − EI-MS; *m/z* (%): 210 (4) [M^+], 179 (7) [M^+ − OMe], 167 (42) [$M^+ - C_3H_7$], 55 (100). − $C_{13}H_{22}O_2$ (210.3): calcd. C 74.24, H 10.55; found C 74.03, H 10.43.

(2E,4R,5R)-4,5,8-Trimethyl-2,7-nonadien-1-ol (**7**): 180 mg (0.86 mmol) of methyl ester **6** were dissolved in 5 ml THF and cooled to −78°C. After the addition of 4.00 ml (4.00 mmol) diisobutylaluminum hydride (1 M solution in hexane) the solution was stirred at −78°C for 1 h and at 0°C for 2 h. Aqueous workup was carried out with 1 N hydrochloric acid. After removal of solvents column chromatography (E/PE 1:2) of the crude product gave 144 mg (92%) of the title compound as a colorless oil. − $[\alpha]_D^{20}$ = −33.0 (*c* = 1.3, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.00 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.25 (t, *J* = 5.5 Hz, 1 H, OH), 1.36−1.54 (m, 1 H), 1.60 (s, 3 H, allylic-CH_3), 1.71 (s, 3 H, allylic-CH_3), 1.73−2.25 (m, 3 H), 4.11 (mc, 2 H, 1-H_2), 5.11 (mc, 1 H, 7-H), 5.52−5.70 (m, 2 H, 2-H, 3-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.93, 17.84, 17.89, 25.85, 32.75, 38.80, 40.40, 63.98, 123.5, 128.4, 131.9, 136.5. − IR (film): ν = 3332, 1668 cm^{-1}. − CI-MS; *m/z* (%): 200 (100) [$M^+ + NH_4^+$]. − $C_{12}H_{22}O$ (182.3): calcd. C 79.06, H 12.17; found C 78.89, H, 12.35.

(2R,3R,4R,5R)- and (2S,3S,4R,5R)-2,3-Epoxy-4,5,8-trimethyl-7-nonen-1-ol (**8**): A solution of 120 mg (0.66 mmol) allylic alcohol **7** and 8.00 mg (0.03 mmol) $VO(acac)_2$ in 4 ml toluene were heated at 90°C when 0.24 ml (0.72 mmol) anhydrous *t*-butyl hydroperoxide were added dropwise. The reaction mixture was heated at 90−100°C for 1 h and cooled to room temp. Aqueous workup was carried out with a saturated Na_2SO_3 solution. After removal of solvents column chromatography (E/PE 1:1) gave 105 mg (80%) of a 2:1 stereoisomeric mixture of 2,3-epoxy alcohols as a colorless oil. − $[\alpha]_D^{20}$ = −3.0 (*c* = 1.2, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.5 Hz, 3 H, CH_3 of major isomer), 0.92 (d, *J* = 6.5 Hz, 3 H, CH_3 of minor isomer), 0.97 (d, *J* = 6.5 Hz, 3 H, CH_3 of minor isomer), 1.05 (d, *J* = 6.5 Hz, 3 H,CH_3 of major isomer), 1.13−1.65 (m, 3 H, 4-H, 5-H, OH), 1.60 (s, 3 H, allylic-CH_3), 1.72 (s, 3 H, allylic-CH_3), 1.78−1.96 (m, 1 H, 6-H), 2.00−2.20 (m, 1 H, 6-H), 2.77 (dd, *J* = 7.5, 2.5 Hz, 1 H, 3-H of minor isomer), 2.83−2.93 (m, 2 H, 2-H, 3-H of major isomer), 2.96 (dt, *J* = 4.0, 2.5 Hz, 1 H, 2-H of minor isomer), 3.55−3.70 (m, 1 H, 1-H), 3.90 (dd, *J* = 12.5, 2.5 Hz, 1 H, 1-H of major isomer), 3.95 (dd, *J* = 12.5, 2.5 Hz, 1 H, 1-H of minor isomer), 5.00−5.20 (m, 1 H, 7-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.25, 16.58, 17.86, 25.86, 32.14, 37.57, 39.73, 56.86, 58.53, 61.94, 123.2, 132.3 (major isomer); δ = 14.97, 16.79, 17.86, 25.86, 32.56, 37.41, 40.16, 59.24, 59.30, 61.65, 122.8, 132.5 (minor isomer). − IR (film): ν = 3418, 1656 cm^{-1}. EI-MS; *m/z* (%): 198 (1) [M^+], 167 (2) [$M^+ - CH_2OH$], 96 (100). − $C_{12}H_{22}O_2$ (198.3): calcd. C 72.68, H 11.18; found C 72.58, H 11.07.

(2R,3R)-2,3,6-Trimethyl-5-hepten-1-ol [(+)-Lasiol] (**1**): 28 mg (0.14 mmol) epoxy alcohol **8** were dissolved in 2 ml 0.5 N KOH (DMSO/H_2O 5:1) and heated at 100°C for 5 h. Aqueous workup and removal of solvents gave 33 mg of crude triol which was dissolved in 4 ml CH_2Cl_2 and treated with 176 mg (0.40 mmol) $Pb(OAc)_4$ and 110 mg (0.80 mg) K_2CO_3 at 0°C for 10 min. Aqueous workup and removal of solvents afforded the crude aldehyde which was dissolved in 2 ml THF-methanol (1:1) and treated with 12 mg (0.30 mmol) $NaBH_4$ at 0°C for 30 min. After aqueous workup and removal of solvents flash chromatography (E/PE 1:2) furnished 10 mg (46% over 3 steps) of (+)-lasiol (**1**) as a colorless oil. − $[\alpha]_D^{20}$ = +12.0 (*c* = 0.4, *n*-hexane). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.93 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.28 (s, 1 H, OH), 1.50−1.65 (m, 2 H, 2-H, 3-H), 1.60 (s, 3 H, allylic-CH_3), 1.70 (s, 3 H, allylic-CH_3), 1.80 (dt, *J* = 14.0, 7.5 Hz, 1 H, 4-H), 2.03 (mc, 1 H, 4-H), 3.46 (dd, *J* = 10.5, 7.0 Hz, 1 H, 1-H), 3.65 (dd, *J* = 10.5, 5.0 Hz, 1 H, 1-H), 5.12 (mc, 1 H, 5-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.83, 17.02, 17.87, 25.90, 31.48, 35.57, 40.31, 66.20, 123.6, 132.1. − IR (film): ν = 3344, 1652 cm^{-1}. − EI-MS; *m/z* (%): 156 (22) [M^+], 123 (32), 95 (43), 82 (54), 69 (100). − $C_{10}H_{20}O$ (156.3): calcd. C 76.86, H 12.90; found C 76.77, H 13.14.

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