Notes

Asymmetric Synthesis of New Chiral Cyclic Ketols

Philippe Renouf, Jean-Marie Poirier,† and Pierre Duhamel*

Université de Rouen-Laboratoire des fonctions azotées oxygénées complexes de l'IRCOF, UPRES A 6014, 76821 Mont Saint Aignan Cedex, France

Received February 24, 1998

Introduction

In our previous work[1,2] we reported an asymmetric enantioselective synthesis of keto enol acetates **2** (>98% ee) bearing a quaternary stereogenic center by enzymatic hydrolysis of prochiral dienol diacetates **1**. In this paper, we now demonstrate that starting from these chiral materials **2**, the synthesis of new enantiopure compounds can be achieved with a total control of the absolute configuration. To test the potential of these new synthons, we chose to prepare stereoisomeric cyclic ketols **3a**−**c** from keto enol acetate **2a** (Schemes 1 and 3). This kind of ketol has been used for the synthesis of bioactive compounds such as Zoapatanol.[3]

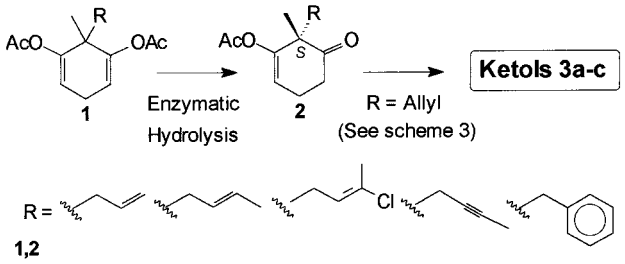
In the literature chiral six-membered ring ketols are prepared by microorganism asymmetric reduction of the corresponding prochiral diketones. This reaction leads to a mixture of two diastereoisomeric alcohols, and ratios depend on diketone substitution. Ketols **3b** and **3d**, with an (*S*) configuration on the stereogenic center bearing the hydroxy group, have been prepared using this methodology (Scheme 2).[4]

Results and Discussion

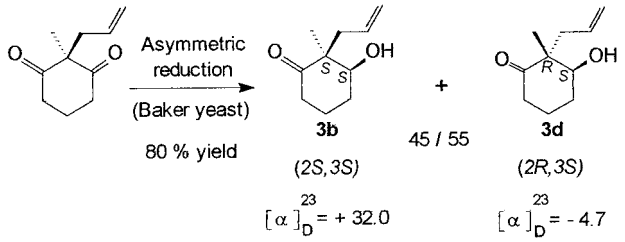
In our preliminary studies, we synthesized ketol **3a** (2*R*,3*R*) to assign the (*S*) absolute configuration to the quaternary stereogenic center of keto acetate **2a**, which had been obtained by enzymatic hydrolysis.[2] Our approach relyied on the $NaBH_4$ reduction of **2a** followed by the cleavage of the enol ester function with methyllithium and purification to afford ketol **3a** (*R*,*R*) in 40% overall yield (Scheme 3).

We have now been able to prepare the (*S*,*S*) enantiomer (ketol **3b**) from the same keto acetate **2a** (Scheme 3). Dioxolane **4** was indeed obtained in good yield from keto

Scheme 1



Scheme 2



acetate **2a**, and subsequent cleavage of the enol ester group by reaction with potassium *tert*-butoxide[5] provided ketone **5**. Alcohol **6b** was then obtained using $LiBHEt_3$ as reducing agent.[6] The major diastereoisomer (1*S*,2*S*/1*R*,2*S*: 96/4) was isolated by chromatography in 91% yield. Compound **6b** was finally converted to ketol **3b** by treatment with 3 N HCl.

For the preparation of ketol **3c** (2*S*,3*R*), diastereoselectivity of carbonyl reduction of the ketone **5** (Scheme 3) has to be inverted. We chose to apply the Luche procedure[7] using a lanthanide chloride derivative as chelating agent. Treatment of ketone **5** with europium trichloride[8] and sodium borohydride in methanol provided a diastereoisomeric mixture out of which alcohol **6c**, presenting (1*R*,2*S*) configuration, was isolated. Hydrolysis with 3 N HCl afforded the ketol **3c**. The configurations of **3a**−**c** prepared as shown in Scheme 3 were attributed according to literature values[4] for **3b** and **3d**.

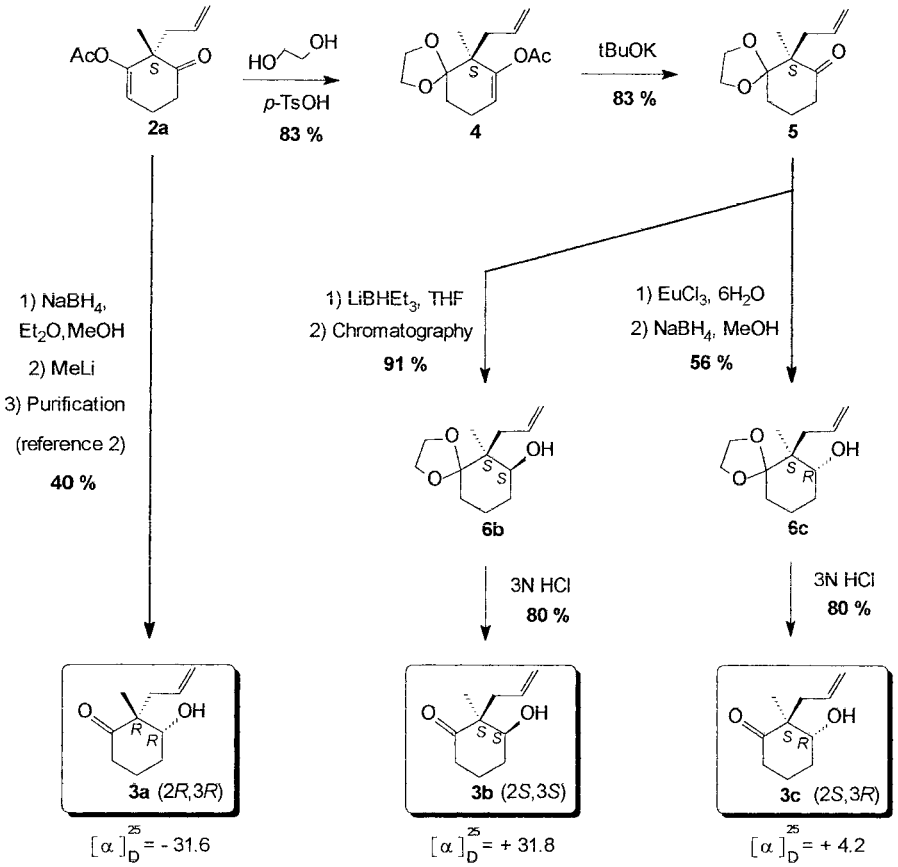
In conclusion, enantiopure ketols **3a**,**c** have been easily synthesized from keto enol acetate **2a** obtained by enzymatic hydrolysis of prochiral dienol diacetate **1a**. Ketol **3c** has never before been prepared to our knowledge. Our methodology which allows the preparation of ketols such as **3a** and **3c**, with an (*R*) configuration for the stereogenic center bearing the hydroxy group, is complementary of the asymmetric reduction of diketones[4] which affords the alcoholic group with an (*S*) configuration. This work is currently being developed on the synthesis of linear enantiomerically pure ketols by transformation of cyclic chiral molecules.

* Corresponding author. E-mail: L.Duhamel@univ-rouen.fr. Phone 33 (0)2 35 52 29 10. Fax 33 (0)2 35 52 24 11.
† Deceased on May, 7, 1997.

(1) Duhamel, P.; Renouf, P.; Cahard, D.; Yebga, A.; Poirier, J. M. *Tetrahedron Asymmetry* **1993**, *4*, 2447−2450.
(2) Renouf, P.; Poirier, J. M.; Duhamel, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1739−1745.
(3) (a) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1985**, *50*, 3411−3414. (b) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huettemann, R.; Kane, V.; Ostrowski, P.; Shaw, C. J. *J. Org. Chem.* **1982**, *47*, 1310−1319.
(4) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223−3232.
(5) Duhamel, P.; Cahard, D.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2509−2511.
(6) Krief, A.; Surleraux, D.; Ropson, N. *Tetrahedron: Asymmetry* **1993**, *4*, 289−292.
(7) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227. (b) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.
(8) Krief, A.; Surleraux, D. *Synlett* **1991**, 273−275.

10.1021/jo980344w CCC: $18.00
Published on Web 03/17/1999

Scheme 3



Furthermore, it is noteworthy that this method can be used as a good tool to produce six-membered cyclic compounds with three stereogenic centers by suitable modifications of the carbonyl moiety of **3a**−**c**.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a spectrometer operating at 200 MHz for ^{1}H and 50 MHz for ^{13}C from $CDCl_3$ solutions unless otherwise noted. *J* values are given in hertz. IR spectra were obtained with a FT-IR spectrophotometer. Mass spectra were recorded on a mass spectrometer (EI: electronic impact; CI: chemical ionization with tBuH). GLC analysis were performed on a gas chromatograph, using an HP-1 (5 m × 0.53 mm × 2.65 μm film) column for GC routine, HP-1 (25 m × 0.25 mm) column for diastereomers separation. Flash chromatography was performed on (230−400 mesh ASTM) silica gel, unless otherwise noted, with petroleum ether (distillation temp < 60 °C)−diethyl ether mixtures as eluent. The progress of reactions was monitored by GC or by TLC (Et_2O−petroleum ether). Microanalyses were performed by the INSA Laboratories, Rouen.

(*S*)-1-Acetoxy-3,3-(ethylenedioxy)-2-methyl-2-(prop-2-enyl)cyclohex-1-ene (4). Keto acetate **2a** (105 mg, 0.5 mmol) was added to a solution of ethylene glycol (0.5 mL, 9 mmol) and *p*-TsOH (5 mg, 0.03 mmol) in benzene (10 mL) and the mixture refluxed for 2 h in a Dean−Stark apparatus. Saturated aqueous $NaHCO_3$ was added. Aqueous layer was extracted with pentane. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (Et_2O/petroleum ether: 15/100) on silica gel (60 Å, > 440 mesh) afforded the dioxolane **4** (106 mg, 83%). ^{1}H NMR δ_H (200 MHz) 1.05 (s,3H), 1.69−1.80 (m,2H), 2.08 (s,3H), 2.30 (dt, *J* 7.2, *J* 1.2, 2H), 3.92−3.97 (m,4H), 4.90−5.01 (m,2H) and 5.37 (t, *J* 4.0, 1H);_^{1}H NMR δ_H (200 MHz, C_6D_6) 1.28 (s,3H), 1.46−1.72 (m,2H), 1.70 (s,3H), 2.01−2.14 (m,2H), 2.55 (dt, *J* 7.3, *J* 1.3, 2H), 3.35−3.50 (m,4H), 5.00−5.17 (m,2H), 5.50 (t, *J* 4.0, 1H), 6.09−6.30 (m,1H);_^{13}C NMR δ_C (50 MHz) 18.4, 20.7, 21.1, 26.9, 40.6, 44.6, 64.6, 64.7, 111.4, 113.9, 115.5, 136.2, 149.5, 169.2; IR (neat) ν_{max} /cm^{-1} 1760, 1640; MS *m*/*z* (EI) 55, 69, 73, 86, 99, 109, 124, 169, 210, 252; $[\alpha]^{25}_D$ (*c* = 1, CH_2Cl_2).

(*S*)-3,3-(Ethylenedioxy)-2-methyl-2-(prop-2-enyl)cyclohexan-1-one (5). A solution of keto acetate **4** (330 mg, 1.3 mmol) in THF (2.5 mL) was added at −20 °C to a suspension of potassium *tert*-butoxide (162 mg, 1.43 mmol) in THF (2.5 mL). The mixture was stirred for 45 min after which 1 N hydrochloric acid and diethyl ether (10 mL) were added to it. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, chromatographed (Et_2O/petroleum ether: 10/100/silica gel: 60 Å, >440 mesh) to afford ketone **5** (230 mg, 83%); ^{1}H NMR δ_H (200 MHz) 1.22 (s, 3H), 1.37−1.78 (m, 4H), 2.00−2.25 (m, 2H), 2.36−2.63 (m, 2H), 3.32−3.37 (m, 4H), 4.92−5.04 (m, 1H); ^{13}C NMR* δ_C (50 MHz) 14.3, 19.3, 29.6, 37.2, 39.3, 58.8, 63.1, 65.3, 113.4, 117.5, 133.5, 211.4; IR (neat) ν_{max} /cm^{-1} 1715, 1640; MS *m*/*z* (CI, tBuH) 99, 211; $[\alpha]^{25}_D$ (*c* = 1, CH_2Cl_2). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.71; H, 8.63; mp 48 °C.

(1*S*,2*S*)-3-(1,3-Dioxolan-2-yl)-2-methyl-2-(prop-2-enyl)cyclohexan-1-ol (6b). To a solution of ketone **5** (210 mg, 1.0 mmol) in THF (5 mL) was added dropwise at − 78 °C a solution of lithium triethylborohydride in THF (1 M in THF, 1.1 mL, 1.1 mmol). The mixture was stirred overnight. Methanol (6 mL) and water (6 mL) were added at − 78 °C, and the mixture was stirred for 30 min. The suspension was concentrated in vacuo, and the residue was dissolved in Et_2O and washed with 1 N hydrochloric acid (acidic pH). The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to afford (210 mg) alcohol **6** in a 96/4 1*S*,2*S*/1*R*,2*S* diastereomeric ratio. The major diastereomer (1*S*,2*S*)-**6b** was obtained by flash chromatography (Et_2O/petroleum ether: 5/100) on silica gel (60 Å, >440 mesh) (195 mg, 91%); ^{1}H NMR δ_H (200 MHz) 0.99 (s, 3H), 1.48−1.76 (m, 6H), 2.00 (dd, *J* 13.3, *J* 8.2, 1H), 3.14 (t, *J* 10.2, OH), 3.60 (dt, *J* 10.2, *J* 3.1, 1H), 3.84−4.00 (m,4H), 5.01−5.13 (m,2H) and 5.78−5.96 (m,1H); ^{13}C NMR δ_C (50 MHz) 17.7, 19.0, 28.0, 30.1, 35.1, 44.9, 64.0, 65.3, 75.5, 112.9, 117.5 and

135.0; IR (neat) ν_{max} /cm^{-1} 3450, 1640; MS *m*/*z* (CI) 195, 213; *m*/*z* (EI) 55, 69, 86, 99, 108, 122, 139, 150, 194, 212.

(1*R*,2*S*)-3-(1,3-Dioxolan-2-yl)-2-methyl-2-(prop-2-enyl)cyclohexan-1-ol (6c). To a solution of ketone **5** (200 mg, 0.95 mmol) in methanol (5 mL) was added at −78 °C europium trichloride (520 mg, 1.4 mmol), and the mixture was stirred for 1 h. Sodium borohydride (36 mg, 0.95 mmol) was added, and the mixture was stirred overnight. Saturated aqueous $NaHCO_3$ (5 mL) was added at −78 °C and then Et_2O (5 mL) at room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to afford (200 mg) alcohol **6** in a 44/56 1*S*,2*S*/1*R*,2*S* diastereomeric ratio. The major diastereomer (1*R*,2*S*)-**6c** was obtained by flash chromatography (Et_2O/petroleum ether: 5/100) on silica gel (60 Å, >440 mesh) (112 mg, 56%); ^{1}H NMR δ_H (200 MHz) 1.00 (s, 3H), 1.49−1.72 (m, 6H), 2.25−2.32 (m, 2H), 2.84 (OH), 3.65−6.72 (m, 1H), 3.85−3.97 (m, 4H), 4.97−5.10 (m, 2H), 5.81−6.02 (m, 1H); ^{13}C NMR δ_C (50 MHz) 15.1, 18.1, 28.1, 29.7, 39.4, 46.0, 64.4, 64.8, 74.0, 113.0, 116.8, 135.8; IR (neat) ν_{max} /cm^{-1} 3540 and 1640; MS *m*/*z* (CI) 195 and 213; *m*/*z* (EI) 55, 69, 86, 99, 108, 122, 139, 150, 194, 212.

Ketols 3b and 3c. Solutions of the alcohols **6b** or **6c** (120 mg, 0.6 mmol) in 3 N hydrochloric acid (4 mL) were stirred overnight at room temperature. The solution was extracted with CH_2Cl_2 (4 × 2 mL), washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (Et_2O/petroleum ether: 20/100) to afford respectively ketols **3b** or **3c** (80 mg, 80%).

(2*S*,3*S*)-3-Hydroxy-2-methyl-2-(prop-2-enyl)cyclohexan-1-one (3b). ^{1}H NMR δ_H (200 MHz) 1.13 (s,3H), 1.60−2.11 (m,-4H), 2.32−2.44 (m, 4H), 2.70 (s,OH), 3.57 (dd, *J* 7.0, *J* 3.3, H), 5.02−5.13 (m,2H), 5.62−5.83 (m,1H);_^{13}C NMR δ_C (50 MHz) 19.5, 20.5, 28.4, 36.4, 37.6, 54.1, 76.3, 117.7, 133.6, 214.5; IR (neat) ν_{max} /cm^{-1} 3480, 1700, 1640; *m*/*z* (CI) 151, 169; MS *m*/*z* (EI) 55, 67, 81, 93, 109, 122, 135, 150, 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59, Found: C, 71.53; H, 9.38; $[\alpha]^{23}_D$ (*c* = 0.48, $CHCl_3$), for comparison Literature[4]: (2*S*,3*S*) **3b**: xxxxx (*c* = 0.42, $CHCl_3$), (2*R*,3*S*) **3d**: $[\alpha]^{23}_D$ (*c* = 0.6, $CHCl_3$).

(2*S*,3*R*)-3-Hydroxy-2-methyl-2-(prop-2-enyl)cyclohexan-1-one (3c). Yield: 80 mg, 80%; ^{1}H NMR δ_H (200 MHz) 1.11 (s,-3H), 1.58−2.07 (m,4H), 2.25−2.45 (m, 4H), 2.82 (s,OH), 3.85 (dd, *J* 7.3, *J* 3.0, H), 5.03−5.12 (m,2H), 5.63−5.84 (m,1H); ^{13}C NMR δ_C (50 MHz) 17.6, 20.3, 28.3, 37.6, 40.0, 54.3, 74.9, 117.8, 133.8, 214.2; IR (neat) ν_{max} /cm^{-1} 3520, 1705, 1645; *m*/*z* (CI) 151 and 169; MS *m*/*z* (EI) 55, 67, 81, 93, 109, 122, 135, 150, 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59, Found: C, 71.53; H, 9.38; $[\alpha]^{25}_D$ (*c* = 0.5, $CHCl_3$). For literature comparison, (2*S*,3*S*) **3b**: $[\alpha]^{23}_D$ (*c* = 0.42, $CHCl_3$); (2*R*,3*S*) **3d**: $[\alpha]^{23}_D$ (*c* = 0.6, $CHCl_3$).

Acknowledgment. We gratefully acknowledge the French Ministère de la Recherche for a grant to P. R.

JO980344W