6α-chloropenicillanates (**7a**)[9] and 6β-chloropenicillanates (**7b**)[10] were previously described.

General Procedure for Catalytic Dehalogenation. The hydrogenolytic reactions were performed at room temperature in a two-necked, round-bottomed flask connected to a hydrogen reservoir maintained at ambient pressure. The catalyst was placed in the flask and flushed with H_2 several times to remove any air.

Method A. In a 5-mL round-bottom flask, fitted with a magnetic stirring bar, 7 mg (ca. 0.006 mmol) of $Pd/CaCO_3$ or Rh/Al_2O_3 and 40 mg (0.4 mmol) of calcium carbonate were suspended in ethyl acetate (0.6 mL). After a period of 20 min of stirring under H_2 at 25 °C (prehydrogenation), Pom 6,6-dihalo- or 6-halopenicillanate (0.05 mmol) dissolved in methanol (1 mL) was added. After the period of time indicated in Table I the solution was filtered through silica gel, and products were identified by TLC and spectroscopic comparison with authentic materials.

Method B. The same procedure was followed as in method A, except the prehydrogenation is carried out in methanol.

Acknowledgment. We thank CONICET (Consejo Nacional de Investigaciones Cientificas y Tecnicas) for financial support and Fellowships (E.L.S. and D.U.B.), Prof. R. A. Corral and J. Zinczuk (Universidad de La Plata) for their generous gift of deuterium, Prof. E. Gross (UMYMFOR) for the low-resolution spectral data. We are also grateful to Dr. John M. Brown and Dr. Eric J. Thomas (University of Oxford, U.K.) for helpful comments on the manuscript.

(9) Setti, E. L.; Mascaretti, O. A. *J. Org. Chem.* **1986**, *51*, 3217.
(10) Belinzoni, D. U.; Setti, E. L.; Mascaretti, O. A. *J. Chem. Res. (S)* **1988**, 176.

Preparation of Stereoisomeric 2,4-Diols: Synthesis and Conformational Study of Bicyclo Derivatives, Isomeric Components of a Pheromone of *Trypodendron lineatum*†

G. Dauphin, A. Fauve, and H. Veschambre*

Laboratoire de Chimie Organique Biologique, U.A. 485 du CNRS, Université Blaise Pascal 63177, Aubière Cedex, France

Received October 27, 1988

In previous work, we showed that acyclic 2,4-diketones could be readily reduced by microbial cells to 2-hydroxy 4-ketones. By appropriate choice of microorganisms, either 2*S* ketols[1] or 2*R* ketols[2] can be obtained, with very high optical purity. These chiral β-hydroxy ketones are useful synthons for the preparation of molecules with several chiral centers. Among them, optically active β-diols are of particular interest. One such molecule, 8-nonene-2,4-diol, can be cyclized to give 1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane, which is the pheromone of the beetle *Trypodendron lineatum*.[3] We report here a novel synthesis of the four stereoisomers of 8-nonene-2,4-diol (**3**) by microbiological reduction of 8-nonene-2,4-dione (**1**) followed by chemical reduction of the two enantiomers of 2-hydroxy-8-nonen-4-one **2**. Subsequent cyclization of each diastereoisomer of **3** gave the four isomers of the pheromone (Scheme I), the structure and conformation of which were analyzed by 1-D and 2-D ^1H and ^{13}C NMR spectroscopy.

† Use of Biological Systems for the Preparation of Chiral Molecules. 6.

Results and Discussion

Synthesis of the Stereoisomers of 8-Nonene-2,4-diol (3). The starting material was 8-nonene-2,4-dione (**1**), easily obtained from pentane-2,4-dione according to Gerlach et al.[4] As already described,[1] 8-nonene-2,4-dione (**1**) is reduced by bakers' yeast (*Saccharomyces cerevisiae*) yielding, after 3 days, (+)-(2*S*)-2-hydroxy-8-nonen-4-one (**2a**) in good yield and an enantiomeric excess close to 99% as shown by GC analysis on a chiral phase.

Two of the diastereoisomers of 8-nonene-2,4-diol were prepared from **2a**. Recently, several methods for the diastereoselective chemical reduction of β-hydroxy ketones have been described. Either the *erythro* or the *threo* diol can be obtained by appropriate choice of reagents.[5,6] We reduced the ketol **2a** using the method of Narasaka et al.,[5c] which gave predominantly the corresponding *erythro* diol. The two diastereoisomers proved easy to separate on a simple silica gel column. Accordingly, rather than use two methods of reduction to obtain each of the diastereoisomers, we carried out a simple reduction of **2a** with $NaBH_4$ and separated the two resulting isomeric diols, obtained in the ratio 54/46, by column chromatography.

Gerlach et al.[4] report that *erythro* 8-methyl-8-nonene-2,4-diol has a higher R_f (0.54) than the *threo* isomer (0.45). For the same diol, Redlich et al.[7] determined the values of the ^{13}C NMR chemical shifts of the carbons bearing the hydroxy groups. Those obtained for the *erythro* isomers were greater than those for the *threo* isomer.

The isomer of 8-nonene-2,4-diol that was eluted first from the column had chemical shift values for the 2 and 4 carbons of 72.1 and 68.7 ppm. The isomer eluted second had corresponding values of 69.3 and 65.6 ppm. By analogy with the results reported for 8-methyl-8-nonene-2,4-diol, we can therefore assign the *erythro* configuration to the diol eluted first. The configuration of the 2 carbon is known to be 2*S*;[1] hence the absolute configuration of this diol is (+)-(2*S*,4*R*)-**3a**. The diol eluted subsequently from the column is therefore (+)-(2*S*,4*S*)-8-nonene-2,4-diol (**3b**) as confirmed by ^1H and ^{13}C NMR analyses. The optical purity of **3a** and **3b** was very high as measured by chromatography on a chiral capillary column[1] (ee >99%).

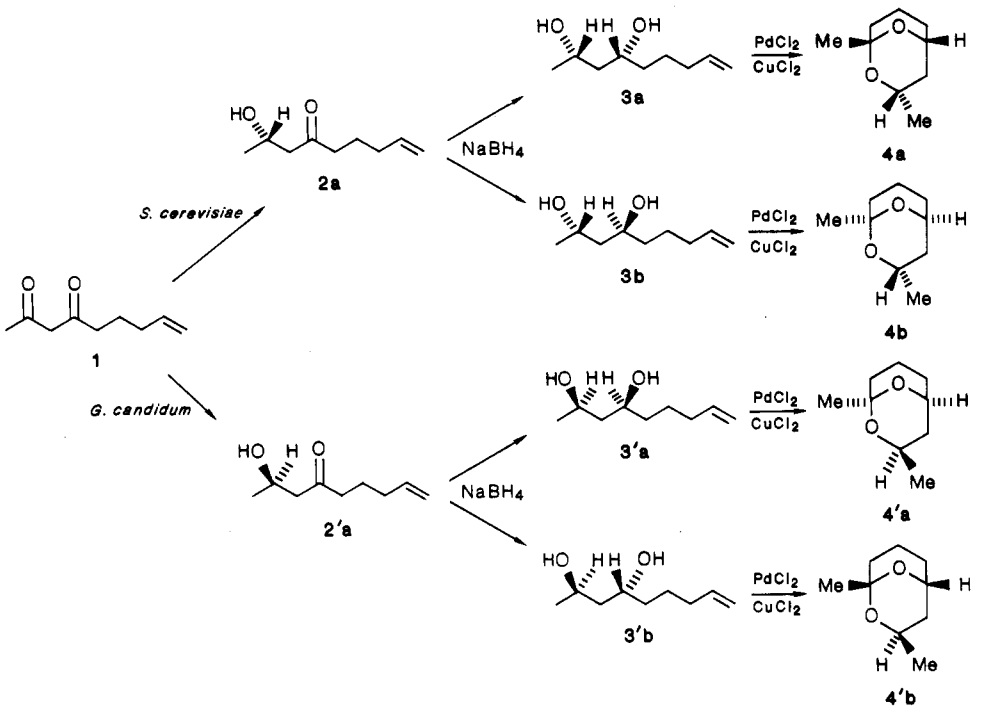
The other two diastereoisomers of 8-nonene-2,4-diol were prepared in the same way starting from 8-nonene-2,4-dione, via the β-hydroxy ketone **2'a** of absolute configuration 2*R*. This hydroxy ketone was obtained by reduction with *Geotrichum candidum* in 70% yield and with 99% enantiomeric excess as already published.[2]

Hydroxy ketone **2'a** was then reduced with $NaBH_4$, giving a mixture of *erythro* and *threo* isomers (58/42) in 77% yield. Separation on a silica gel column yielded the *erythro* isomer first. Its configuration was confirmed by ^{13}C NMR. The configuration of the 2 carbon is known to be 2*R*;[2] hence the absolute configuration of the diol is (−)-(2*R*,4*S*)-**3'a**. The diol eluted subsequently was therefore (−)-(2*R*,4*R*)-8-nonene-2,4-diol (**3'b**). Both **3'a** and **3'b** were optically pure as measured by chromatography on a chiral capillary column.

(1) Bolte, J.; Gourcy, J. G.; Veschambre, H.; *Tetrahedron Lett.* **1986**, *27*, 565.
(2) Fauve, A.; Veschambre, H. *J. Org. Chem.* **1988**, *53*, 5215.
(3) Kongkathip, B.; Kongkathip, N. *Tetrahedron Lett.* **1984**, *25*, 2175.
(4) Gerlach, H.; Kunzler, F. *Helv. Chim. Acta* **1977**, *60*, 638.
(5) (a) Chen, K. M.; Hardtman, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155. (b) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Ibid.* **1986**, *27*, 3009. (c) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233.
(6) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.
(7) Redlich, H.; Schneider, B.; Hoffman, R. W.; Geuke, K. J. *Justus Liebigs Ann. Chem.* **1983**, 393.

0022-3263/89/1954-2238$01.50/0

Scheme I



The ease with which all four diastereoisomers of 8-nonene-2,4-diol can be prepared from the same starting material further illustrates the usefulness of microbiological reduction.

Synthesis of the Stereoisomers of the Pheromone Components of *T. lineatum*. Kongkathip et al.[3] have shown that racemic 8-nonene-2,4-diol can be cyclized to give 1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane. This substance has been isolated from Norway spruce infested by the parasite *T. lineatum*. It has been suggested[8] that it serves as a primary attractant for this species. This pheromone has already been synthesized by various means; some routes have given racemates,[3,9] others, including that of Redlich et al.,[7] give the four optically active diastereoisomers from a sugar and after many steps.

We obtained the four isomers of the pheromone by cyclization of each of the 8-nonene-2,4-diols previously obtained. The reaction was carried out by the method of Kongkathip et al.[3] using palladium chloride in the presence of cupric chloride.

(2*S*,4*R*)-8-Nonene-2,4-diol (**3a**) gave (+)-(1*S*,3*S*,5*R*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**4a**) with a yield of about 30%. Its ^{1}H NMR spectrum at 300 MHz and its optical rotation agree with those reported in the literature.[7] The three other isomers of 8-nonene-2,4-diol were cyclized under the same conditions, giving the other three stereoisomers with similar yields. Their ^{1}H NMR spectra and optical rotations agree with those reported in the literature.[7]

This synthetic route (three steps for each isomer) is much more rapid than that described by Redlich,[7] which requires about ten steps, with a final cyclization step giving similar yields. As we went to press, Ohta et al.,[10] using a method similar to ours, reported the preparation of only one isomer of the pheromone ((1*S*,3*S*,5*R*)-**4a**).

(8) Heemann, V.; Francke, W. *Naturwissenshaften* **1976**, *63*, 344. *Planta Med.* **1977**, *32*, 342.
(9) (a) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *Tetrahedron Lett.* **1986**, *27*, 3535. (b) Moar, P.; Tamm, C. *Ibid.* **1987**, *28*, 395. (c) Guindon, Y.; St. Denis, Y.; Daigneault, S.; Morton, H. E. *Ibid.* **1986**, *27*, 1237.
(10) Ohta, H.; Ozaki, K.; Tsuchiashi, G. *Chem. Lett.* **1987**, 2225.

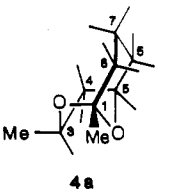
Table I. Apparent Coupling Constants (Hz) of 4a and 4b

proton pair[a]	4a ^3J	4b ^3J
3-Me	6.0 a–e	6.0 a–e
3–4A	5.0 a–e	11.0 a–e
3–4B	11.0 a–a	3.8 a–e
4A–4B	13.5	13.5
4A–5e	10.0 e–e	5.0 a–e
4B–5e	3.0 a–e	1.0 e–e
5–6Be	3.0	4.0
5–6Aa		4.0
6Aa–6Be	13.5	13.5
6A–7A	12.6 a–a	10.0
6A–7B	4.0 a–e	
7A–8A	6.0 a–e	5.0
7A–8B	13.0 a–a	9.0
7B–8B	6.5 e–a	5.0
7B–8A	1.0 e–e	2.0
8A–8B	14.5	13.5

[a] The codings A and B refer respectively to the proton at lowest and highest field side.

NMR Spectroscopic Studies. The structure and conformation of the isomers **4a** and **4b** were studied by using 1-D and 2-D ^{1}H and ^{13}C NMR spectroscopy. ^{1}H–^{1}H homonuclear chemical shift correlation (COSY) and ^{1}H–^{13}C heteronuclear chemical shift correlation gave ^{1}H and ^{13}C NMR peak assignments (Figure 1).

^{1}H–^{1}H coupling constants reported in Table I were obtained directly from the ^{1}H–^{1}H spectrum, via double resonance experiments or from COSY experiments. ^{1}H–^{1}H coupling constants and NOESY experimental results showed the prefered conformation of **4a** and **4b**.



4a

Isomer 4a. For the ring I (1,3-dioxane ring), the following coupling constants were found for protons H_3 and H_4 (Table I): $J_{3,4B}$ = 11.0 Hz and $J_{3,4A}$ = 5.0 Hz, showing

that H_3 and H_{4B} are axial and H_{4A} is equatorial. The ring I thus has a boat conformation. This is confirmed by the high value of the coupling constant for the syn H_{4Ae} and H_{5e} protons (10.0 Hz) (dihedral angle # 0°) and by the NOE effect between H_3–Me_1 and H_5–H_{4Ae}.

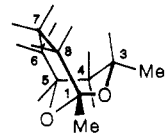
For the ring II (tetrahydropyran ring), the following coupling constants were found: $J_{6A,7A}$ = 12.6 Hz and $J_{7A,8B}$ = 13.0 Hz. These values show that the protons are axial and antiperiplanar. Hence the ring II has a chair conformation. This is confirmed by the NOE effect between H_{6Aa} and H_{8Ba}.

The preferred conformation of isomer **4a** is therefore the following: ring I, boat conformation; ring II, chair conformation with the 3-methyl equatorial. In this conformation the NOE effect possible between H_{4a} and H_{7a} is observed.

Isomer 4b. For the ring I, the following coupling constants were found: $J_{3,4A}$ = 11.5 Hz; $J_{3,4B}$ = 3.8 Hz; $J_{4A,5}$ = 5.0 Hz, and $J_{4B,5}$ = 1.0 Hz. These values show that H_3 and H_{4A} are axial and that the ring I has a chair conformation with dihedral angles of 50° and 70° for H_{4Aa}–H_5 and H_{4Be}–H_5.

For the ring II, the coupling constants were as follows: $J_{6A,7A}$ = 10.0 Hz; $J_{7A,8B}$ = 9.0 Hz; $J_{5,6A}$ = $J_{5,6B}$ = 4.0 Hz. These values show that H_{6A} is nearly antiperiplanar to H_{7A} and that H_{7A} is nearly antiperiplanar to H_{8B}. Thus the ring II has a half-chair conformation with the oxygen at the top. The coupling constants for H_5, H_{6A}, and H_{6B} indicate dihedral angles of 60° for H_5–H_{6A} and H_5–H_{6B}.

The preferred conformation of **4b** is therefore the following: ring I in the chair conformation, ring II in the half-chair conformation and the 3-methyl equatorial. This conformation is consistent with the NOE effects observed between H_{3a} and H_{8a}. The signal of the H_3 proton in **4b** is shifted downfield by 0.66 ppm compared with the same proton in **4a**, as a result of steric compression.



4b

The conformations of **4a** and **4b** are quite different; **4b** being more compact than that of **4a**. In addition, the difference in chemical shift between the 7 carbon of **4a** and that of **4b** is consistent with the conformations proposed. The 7 carbon of **4a** is shifted upfield by 5.4 ppm. This is due to the "γ-gauche" effects of the C_1–O bonds, which are absent in **4b**.

Conclusion

To conclude, we report here a novel method for the easy preparation of diastereoisomeric diols from a 2,4-dione. The key step is the selective microbiological reduction of the dione to each of the enantiomeric β-hydroxy ketones. Cyclization of the diols provided all the isomers of a pheromone, which was thereby obtained in fewer steps than hitherto. The naturally occurring substance corresponds to either **4a** or enantiomer **4'a**.[8] The structures and conformations of the diastereoisomers were studied and proved to be appreciably different.

Experimental Section

General Methods. Analytical gas chromatography was performed on a capillary column filled with 20% Carbowax (20 m × 0.32 mm). The carrier gas was helium at 1.2 kg/cm^2. Retention times of the products were compared to those of racemic samples obtained by chemical methods. Enantiomeric excesses were determined by chromatography using a 26 m × 0.22 mm capillary column packed with Chirasil-L-valin as described.[1]

Thin layer chromatography was performed on Schleicher and Schuell F 1500/LS with hexane/ethyl acetate (60/40) or pentane/ether (90/10) as eluents I and II, respectively. Column chromatography was performed on Amicon silica gel (70–200 mesh) with the same eluent as in thin layer chromatography. Purification of each compound was carried out by bulb-to-bulb distillation.

Optical rotation values were determined at 25 °C for the mercury J line (λ = 578 nm). No elemental analyses were performed. The products obtained being already described, analysis of their retention time, NMR spectra, and optical rotation values is considered sufficient for identification.

Culture conditions for *G. candidum* (CBS 233-76) have been described previously.[11]

NMR Spectra. NMR spectra were recorded in $CDCl_3$ solution at 60 and 300 MHz for ^1H; 15.03 and 75.47 MHz for ^{13}C. For ^{13}C modulated spin–echo spectra, a composite pulse was used.

^1H–^1H Chemical Shift Correlation [COSY][12,13] for 4a and 4b. The applied pulse sequence was ($\pi/2$)–(t_1)–($\pi/4$)–(FID, t_2); the spectral width in F_1 and F_2 was 1176 Hz for **4a** and 1272 Hz for **4b**; and the number of data points in t_2 was 2048 and 256 increments were performed (NS = 64). Before Fourier transformation and symmetrization, the data were multiplied with a sine-bell. The $\pi/2$ pulse width was 8.5 μs.

^1H–^1H Chemical Shift Correlation [NOESY][14] for 4a and 4b. The applied pulse sequence was ($\pi/2$)–(t_1)–($\pi/2$)–(t_m)–($\pi/2$)–(FID, t_2) with t_m = 0.4 s (pseudo random variation of 20%). The other spectral parameters were the same as in COSY experiments.

^1H–^{13}C Chemical Shift Correlation[12,15] for 4a and 4b. The applied pulse sequence was ($\pi/2$, ^1H)–($t^1/2$)–(π, ^{13}C)–($t^1/2$)–(τ_1)–($\pi/2$, ^1H; $\pi/2$, ^{13}C)–(τ_2)–(BB, ^1H, FID, t_2) with τ_1 = 0.00357 s and τ_2 = 0.001785 s. The spectral width in F_1 was 1176 Hz and 1272 Hz and in F_2 6666Hz and 5494 Hz for **4a** and **4b**, respectively; the number of data points in t_2 was 2048 and 128 increments were performed (NS = 152). Before Fourier transformation, the data were multiplied with unshifted sine-bell in F_2 and exponential in F_1. The $\pi/2$ pulse width was 7 μs for ^{13}C and the decoupler $\pi/2$ pulse width was 9 μs.

8-Nonene-2,4-dione (1). 8-Nonene-2,4-dione (**1**) was prepared from pentane-2,4-dione (4 g) and 1-bromo-4-butene (5.5 g) by the method of Gerlach et al.[4] Purification on a silica gel column (eluent II) gave 2.5 g (40%) of 8-nonene-2,4-dione as a colorless oil. ^1H NMR, 60 MHz: δ 1.30 to 2.80 (m, 8 H), 2.05 (s, 3 H), 4.80 to 5.20 (m, 2 H), 5.50 to 6.20 (m, 1 H). ^{13}C NMR, 15.03 MHz: δ 191.9, 191.4, 137.8, 115.3, 99.9, 37.5, 33.1, 25.0, 24.8.

(+)-(2*S*)-2-Hydroxy-8-nonen-4-one (2a). Diketone **1** (2 g) was reduced by 200 g of bakers' yeast (Hirondelle brand) suspended in 4 L of aqueous sucrose (30 g/L). The mixture was stirred and kept at 35 °C for 3 days. After 24 h and 48 h, however, 60 g of sucrose was added. After centrifuging, the aqueous phase was continuously extracted with ether for 24 h. The residue was purified on a silica gel column (eluent II). Bulb-to-bulb distillation (oven temperature: 230 °C) gave 1.4 g (70%) of 2-hydroxy-8-nonen-4-one (**2a**) as a colorless oil. TLC, R_f: 0.5. GC, retention time 7.8 min; oven temperature 140 °C. ^1H NMR, 60 MHz: δ 1.20 (d, 3 H, J = 7 Hz), 1.40 to 2.60 (m, 8 H), 3.15 (s, 1 H exchanged with D_2O), 4.10 to 4.50 (m, 1 H), 4.80 to 5.30 (m, 2 H), 5.50 to 6.10 (m, 1 H). $[\alpha]^{25}_D$ + 58° (c = 0.05, $CHCl_3$) [lit.[1] $[\alpha]^{25}_D$ +58.5°]. ee: 99%.

(+)-(2*S*,4*R*)- and (+)-(2*S*,4*S*)-8-Nonene-2,4-diol (3a and 3b). In a 50-mL flask, 3.5 mL of 0.05 N KOH, 0.4 g of $NaBH_4$, and 1.1 g of hydroxy ketone **2a** were heated together for 30 min on a water bath at 50 °C. Glycerol (3.5 mL) was then added and

(11) Belan, A.; Bolte, J.; Fauve, A.; Gourcy, J. G., Veschambre, H. *J. Org. Chem.* **1986**, *52*, 256.
(12) Bax, A. *Two Dimensional Nuclear Magnetic Resonance in liquids*; Delft University Press: London, 1982.
(13) (a) Bax, A.; Freeman, R.; Morris, G. *J. Magn. Reson.* **1981**, *42*, 1981. (b) Bax, A.; Freeman, R. *Ibid.* **1981**, *44*, 542.
(14) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546.
(15) (a) Bodenhausen, G.; Freeman, R. *J. Magn. Reson.* **1977**, *26*, 471. (b) Freeman, R.; Morris, G. *J. Chem. Soc., Chem. Commun.* **1978**, 684.

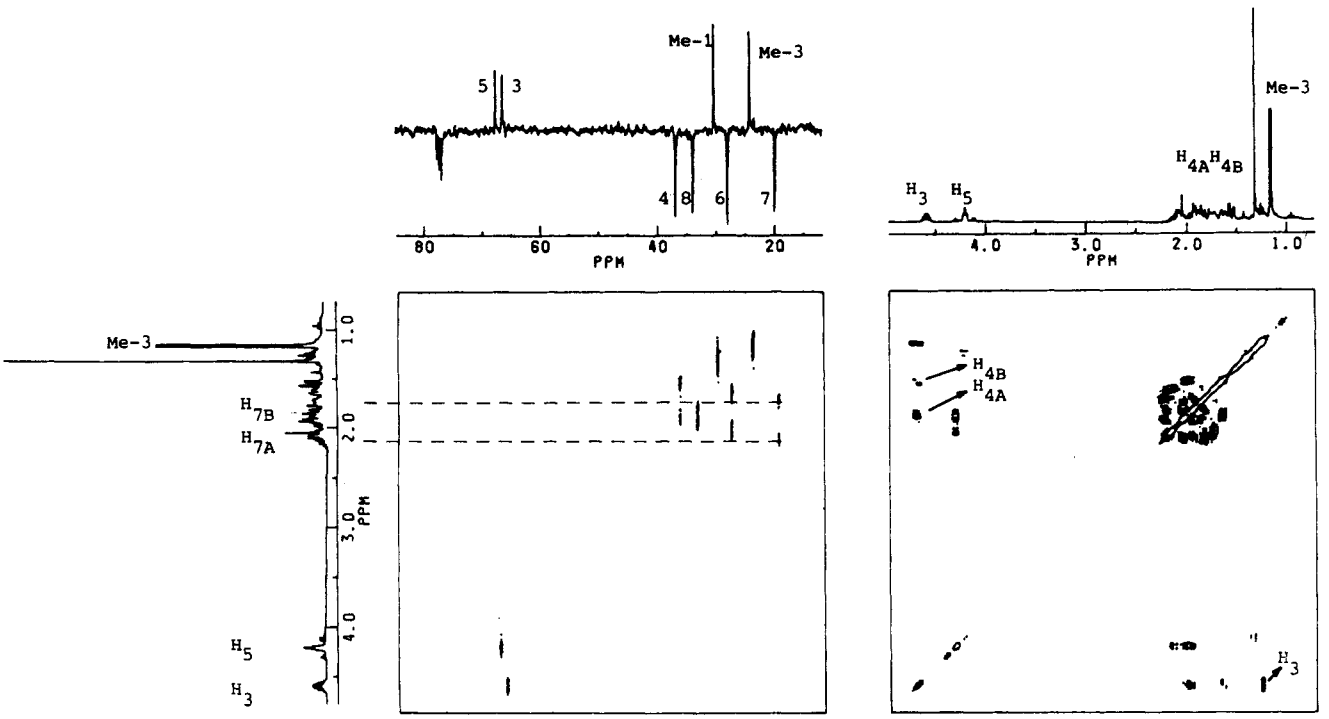


Figure 1. ^1H–^{13}C heteronuclear chemical shift correlation and ^1H–^1H homonuclear chemical shift correlation (COSY) for **4b**.

heating was continued for 30 min at 80 °C. After cooling, the mixture was diluted with water and extracted four times with ethyl acetate. The extracts were dried and evaporated down to a residue (1 g) containing roughly equal amounts of diols **3a** and **3b**, which were separated by column chromatography (100 g silica gel) with eluent I.

3a: 0.500 g (45%), colorless oil. TLC, R_f: 0.55. ^1H NMR, 300 MHz: δ 1.13 (d, J = 6 Hz, 3 H), 1.31 to 1.63 (m, 6 H), 1.92 to 2.07 (m, 2 H), 3.77 (m, 1 H), 3.97 (m, 1 H), 4.19 (s, 2 H exchanged with D_2O), 4.86 to 5.01 (m, 2 H), 5.67 to 5.82 (m, 1 H). ^{13}C NMR, 75.47 MHz: δ 138.56 (C8), 114.50 (C9), 72.13 (C2 or C4), 68.70 (C2 or C4), 44.50 (C3), 37.46 (C7), 33.58 (C5), 24.55 (C6), 23.96 (C1). $[\alpha]^{25}_J$ + 14° (c = 0.02, $CHCl_3$). ee > 99%.

3b: 0.380 g (35%), colorless oil. TLC, R_f: 0.40. ^1H NMR, 300 MHz: δ 1.25 (d, J = 6 Hz, 3 H), 1.35 to 1.67 (m, 6 H), 2.04 to 2.15 (m, 2 H), 2.64 (s, 2 H, exchanged with D_2O), 3.95 (m, 1 H), 4.17 (m, 1 H), 4.93 to 5.08 (m, 2 H), 5.73 to 5.90 (m, 1 H). ^{13}C NMR, 75.47 MHz: δ 138.69 (C8), 114.75 (C9), 69.30 (C2 or C4), 65.61 (C2 or C4), 44.22 (C3), 38.95 (C7), 33.72 (C5), 25.14 (C6), 23.68 (C1). $[\alpha]^{25}_J$ +20° (c = 0.03, $CHCl_3$). ee > 99%.

The combined yield was 80%.

(+)-(1*S*,3*S*,5*R*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (4a). A suspension of 0.155 g of 8-nonene-2,4-diol (**3a**) in 20 mL of anhydrous THF, 0.04 g of $PdCl_2$, and 0.1 g of $CuCl_2$ was stirred at ambient temperature for 10 h and the mixture was then filtered on a small column filled with a mixture of 10 g of $MgSO_4$ and 10 g of silica gel to remove salts. The column was thoroughly washed with ether. After drying, the solvent was evaporated off on a water bath at 40 °C. The residue was purified on a silica gel column with eluent II. Bulb-to-bulb distillation (oven temperature 250 °C) afforded 0.045 g of **4a** (30%) as a colorless oil. TLC, R_f: 0.8. ^1H NMR, 300 MHz: δ 1.19 (d, J = 6 Hz, 3 H), 1.27 (s, 3 H), 1.31 to 1.83 (m, 6 H), 2.01 to 2.18 (m, 2 H), 3.89 to 4.01 (m, 1 H), 4.20 to 4.33 (m, 1 H). ^{13}C NMR, 75.47 MHz: δ 97.5 (C1), 66.9 (C5), 61.5 (C3), 37.1 (C4), 34.9 (C8), 29.8 (C6), 27.4 (1-Me), 21.0 (3-Me), 14.4 (C7). $[\alpha]^{25}_J$ +37.4° (c = 0.02, pentane) [lit.[7] $[\alpha]^{22}_D$ + 37.5°].

(−)-(1*R*,3*S*,5*S*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (4b). The cyclization was carried out under the same conditions as above from 0.320 g of **3b** in 40 mL of anhydrous THF, in the presence of 0.05 g of $PdCl_2$ and 0.120 g of $CuCl_2$. The solvent was evaporated off leaving a residue that was purified as for **4a**; bulb-to-bulb distillation (oven temperature 250 °C) afforded 0.085 g of **4b** (32%) as a colorless oil. TLC, R_f: 0.5 (eluent II). ^1H NMR, 300 MHz: δ 1.16 (d, J = 6 Hz, 3 H), 1.31 (s, 3 H), 1.50 to 2.00 (m, 6 H), 2.00 to 2.20 (m, 2 H), 4.13 to 4.30 (m, 1 H), 4.50 to 4.65 (m, 1 H). ^{13}C NMR, 75.47 MHz: δ 95.3 (C1), 67.4 (C5), 66.2 (C3), 36.8 (C4), 33.8 (C8), 30.2 (1-Me), 27.9 (C6), 24.1 (3-Me), 19.8 (C7). $[\alpha]^{25}_J$ −4° (c = 0.04, pentane) [lit.[7] $[\alpha]^{22}_D$ −4.4°].

(−)-(2*R*)-2-Hydroxy-8-nonen-4-one (2′a). After 48 h of growth, a culture of *G. candidum*[11] (1 L) was filtered and the mycelium (80 g) was washed repeatedly with NaCl solution (8 g/L). Wet mycelium (5 g) was suspended in 500-mL conical flasks containing 50 mL of 5% glucose solution and 50 μL of 8-nonene-2,4-dione (**1**). The flasks were shaken at 200 rpm at 27 °C for 10 h. The mixture was filtered and the filtrate was extracted continuously with ether overnight. After drying and evaporating the solvent, the residue was purified by column chromatography (eluent II). Bulb-to-bulb distillation (oven temperature 230 °C) gave 0.560 g (70%) of hydroxy ketone **2′a** as a colorless oil. TLC, R_f: 0.5. GC, t_R 7.8 min; oven temperature 140 °C. ^1H NMR spectrum identical with that obtained for **2a**. $[\alpha]^{25}_J$ −56° (c = 0.05 $CHCl_3$) [lit.[2] $[\alpha]^{25}_J$ −55°]. ee 98%.

(−)-(2*R*,4*S*)- and (−)-(2*R*,4*R*)-8-Nonene-2,4-diol (3′a and 3′b). The reduction of the ketol **2′a** was carried out under the same conditions as previously described for **2a**. From 1 g of **2′a** 0.9 g of residue was obtained, containing the two diastereoisomeric diols. They were separated and purified by column chromatography (eluent I).

3′a: colorless oil, yield, 0.460 g (45.5%). TLC R_f: 0.55. ^1H and ^{13}C NMR spectra identical with those of enantiomer **3a**. $[\alpha]^{25}_J$ −13.7° (c = 0.05 $CHCl_3$). ee 98%.

3′b: colorless oil, yield 0.320 g (31.5%). TLC R_f: 0.40. ^1H and ^{13}C NMR spectra identical with those of enantiomer **3b**. $[\alpha]^{25}_J$ −19.7° (c = 0.07, $CHCl_3$). ee 98%.

The combined yield of reduction was 77%.

(−)-(1*R*,3*R*,5*S*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (4′a). The cyclization was carried out as previously from 0.290 g of **3′a** in 50 mL of THF in the presence of 0.05 g of $PdCl_2$ and 0.120 g of $CuCl_2$, after 10 h of stirring, 0.089 g (30%) of **4′a** was obtained as a colorless oil. TLC R_f: 0.8 (eluent II). ^1H and ^{13}C NMR spectra identical with those of enantiomer **4a**. $[\alpha]^{25}_J$ −37.2° (c = 0.02 pentane) [lit.[7] $[\alpha]^{22}_D$ −37.3°].

(+)-(1*S*,3*R*,5*R*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (4′b). From 0.220 g of diol **3′b** in 35 mL of anhydrous THF, in the presence of 0.045 g of $PdCl_2$ and 0.110 g of $CuCl_2$ after 10 h of stirring, 0.07 g (34%) of **4′b** was obtained as a colorless oil. TLC R_f: 0.5 (eluent II). ^1H and ^{13}C NMR spectra identical with those of enantiomer **4b**. $[\alpha]^{25}_J$ = +4.2° (c = 0.03, pentane) [lit.[7] $[\alpha]^{22}_D$ +4.7°].

Acknowledgment. A special thanks to Dr. M. F. Renard for skillful help in structure elucidation.

Registry No. 1, 91273-98-2; **2a**, 102273-62-1; **2'a**, 116531-36-3; **3a**, 108508-58-3; **3'a**, 119785-58-9; **3b**, 108508-56-1; **3'b**, 119785-59-0; **4a**, 76740-35-7; **4'a**, 76740-34-6; **4b**, 76740-36-8; **4'b**, 76334-10-6.

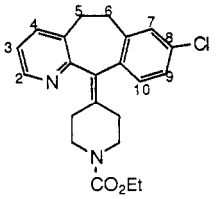
Superacid Cyclodehydration of Ketones in the Production of Tricyclic Antihistamines

Doris P. Schumacher,* Bruce L. Murphy, Jon E. Clark, Pete Tahbaz, and Thomas A. Mann

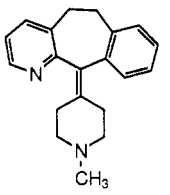
Chemical Process Research, Schering-Plough Corporation, Bloomfield, New Jersey 07003

Received October 11, 1988

Loratadine (Sch 29851; 1) is a potent, long-acting antihistamine with a lack of central nervous system (CNS) side effects.[1] Although the compound is a derivative of azatadine (2), the presence of a chlorine in the phenyl ring causes unique problems such that the azatadine process, which requires two reduction steps, cannot be effectively used, as the chlorine is in part removed.[2] In addition, formation of the tricyclic ring structure with polyphosphoric acid results in isomers chlorinated in the 8- or 10-position. These problems were previously overcome by use of an inefficient alkylation/reduction process (yield <35%), a Friedel–Crafts acylation, and a Grignard reaction which gave greater than 30% of undesired 1,6-addition products. The overall yield for this process was ~4%.



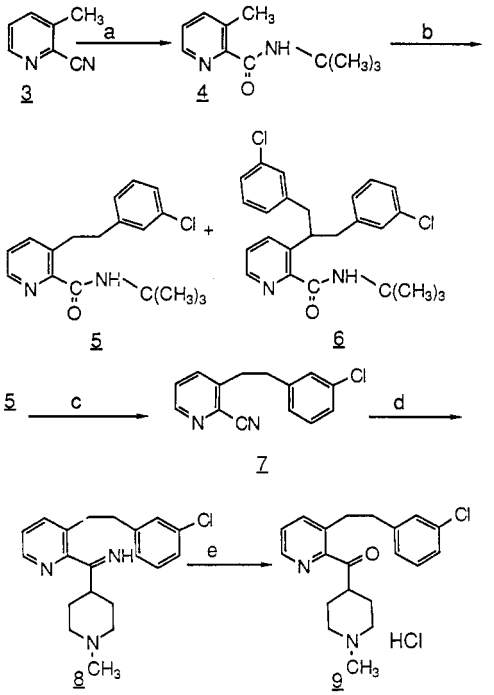
1
LORATADINE



2
AZATADINE

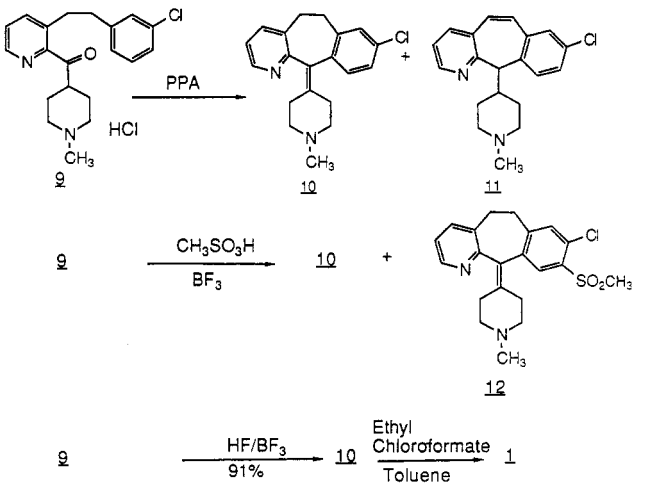
The requirement for large quantities of loratadine necessitated the practical and economical introduction of the piperidine ring as well as formation of the tricyclic ring structure. Initially, the alkylation of 2-cyano-3-methylpyridine (3) was addressed (Scheme I). Direct alkylation of 3 with *m*-chlorobenzaldehyde gave low yields due to self-condensation of the nitrile. McOmie[3] suggests that a nitrile might be protected as the *tert*-butylamide formed via a Ritter reaction.[4] Such protection proved effective, and the *tert*-butylamide 4 was formed in 97% yield with *tert*-butyl alcohol and sulfuric acid. The dianion of this amide was readily formed with *n*-butyllithium at −30 °C, the compound itself serving as an indicator for the titration of the base.[5] The dianion was alkylated with *m*-chlorobenzyl chloride to give the (chlorophenethyl)pyridine 5 in

Scheme I[a]



[a] (a) H_2SO_4, *t*-BuOH; (b) *n*-BuLi, *m*-chlorobenzyl chloride, THF; (c) $POCl_3$; (d) (*N*-methylpiperidyl)magnesium chloride, THF; (e) aqueous HCl.

Scheme II



92% yield. A small amount of dialkylated byproduct 6 was also obtained.

The amide 5 was converted to nitrile 7 with phosphorus oxychloride in 94% yield after crystallization. Formerly, ring closure was effected at this point to provide a ketone, followed by alkylation with (*N*-methylpiperidyl)magnesium chloride and dehydration with sulfuric acid. As an alternative, we investigated the addition of the Grignard reagent to the nitrile to form a ketone, followed by cyclodehydration to give 8-chloroazatadine. The nitrile was alkylated with (*N*-methylpiperidyl)magnesium chloride to give the imine 8, which could be isolated and subsequently converted to loratadine. However, we found that hydrolysis of the imine in situ with hydrochloric acid led to the convenient and efficient recovery of ketone hydrochloride 9 in 91% yield. No 1,6-addition of the Grignard reagent was observed.

The crux of this procedure is the cyclodehydration of the ketone to the penultimate azatadine derivative 10

(1) Kreutner, W.; Chapman, R. W.; Gulbenkian, A.; Siegel, M. I. *Allergy (Copenhagen)* **1987**, *42*, 57–63. Barnett, A.; Iorio, L. L.; Kreutner, W.; Tozzi, S.; Ahn, H. S.; Gulbenkian, A. *Agents Actions* **1984**, *14*, 590–597.

(2) (a) Villani, F. J. U.S. Patent 3326924, 1967. (b) Villani, F. J.; Wefer, E. A.; Mann, T. A.; Mayer, J.; Peer, L.; Levy, A. S. *J. Heterocycl. Chem.* **1972**, *9*, 1203–1207. (c) Villani, F. J.; Daniels, P. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C.; Wefer, E. A. *J. Med. Chem.* **1972**, *15*, 750–754.

(3) McOmie, J. F. W. *Protective Groups in Organic Chemistry*; Plenum Press: New York, 1973; p 409.

(4) For a review of the Ritter reaction, see: Krimen, L. I.; Cota, D. J. *Org. React. (N.Y.)* **1969**, *17*, 213–325.

(5) Compound 4 serves as an excellent indicator for organolithium reagents. An intense purple color appears immediately upon formation of the dianion.

0022-3263/89/1954-2242$01.50/0