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Total synthesis of racemic lasidiol via intramolecular [4+3] cycloaddition

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Abstract

Lasidiol, a sesquiterpenoid with a carotane skeleton, and its 8a-epimer have been synthesized in 12 steps starting from 2-methylfuran. Key elements in the synthesis are constructions of the carbon framework in an intramolecular [4+3] cycloaddition and cleavage of the epoxy-bridge by reductive elimination with sodium naphthalenide after reduction and hydrogenation of the bromo-substituted cycloadducts. © 2000 Elsevier Science Ltd. All rights reserved.

The carotane skeleton is found in a variety of naturally occurring sesquiterpenoids.[1a] Well-known representatives of the carotanes (often called daucanes, too) are carotol and siol acetate[1b] with a *cis*-fused ring system. To date, only a few strategies for the construction of the carotane framework have been reported,[2a–e] among them three different routes[2a–c] to daucene, the simplest sesquiterpene of this type.

In connection with our program to explore the utility of the [4+3] cycloaddition for the synthesis of sesquiterpenoids, our attention was drawn to the carotane lasidiol (**1**). Its oxygen functionality in the seven-membered ring nicely accommodates the substitution pattern engendered by the [4+3] cycloaddition. Lasidiol angelate was isolated from the leaves of *Lasiantheae fruticosa* (Compositae).[3]

Our retrosynthetic strategy for the synthesis of lasidiol (**1**) is outlined in Scheme 1. Key elements are: (i) construction of an epoxy-bridged hydroazulene skeleton with a halogen substituent in β-position to the ether linkage via intramolecular [4+3] cycloaddition;[4] and (ii) cleavage of the oxygen-bridge by reductive elimination, which has recently been explored in detail in this laboratory.[5,6]

The intramolecular [4+3] cycloaddition with oxyallyls and 1,3-dienes, which has been reviewed recently,[4c] has increasingly received attention from mechanistic and synthetic interests and its utility has been demonstrated in natural products synthesis.[7]

The synthesis of the required dibromo ketone **8** is shown in Scheme 2. Starting material was the ketone **2**, which is readily available via Friedel–Crafts acylation from 2-methylfuran and isobutyric

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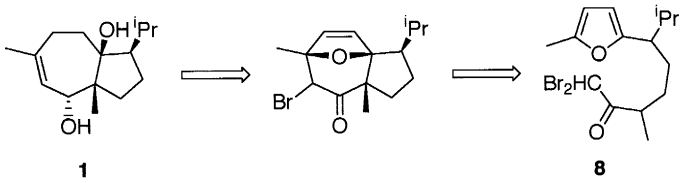
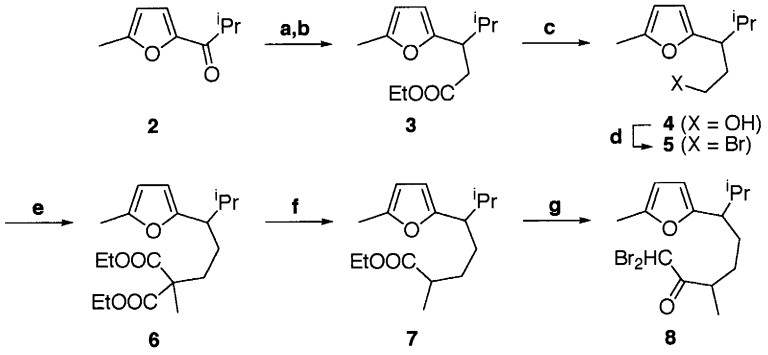


Scheme 1.

anhydride.[8] Wittig–Horner reaction[9] of **2** afforded a 1:4 mixture of *E* and *Z* furyl acrylic esters, which was catalytically hydrogenated to give the ester **3**. This was reduced with lithium aluminum hydride in diethyl ether, and the alcohol **4** converted to the bromide **5** with triphenylphosphine and tetrabromomethane.[10] Quite unexpectedly, alkylation[11] of the lithium enolate from ethyl propionate in THF/HMPA at −78 °C with **5** to give **7** failed to occur in a number of experiments, and only the starting material was recovered. Therefore, the desired ester **7** was prepared from **5** by malonic ester synthesis with the sodium enolate from diethylmethylmalonate in DMF, followed by decarbalkoxylation[12] of the diester **6**. Finally, reaction of **7** with in situ generated dibromomethyllithium[13] provided the dibromo ketone **8** as a 1:1 mixture of the two diastereomers.



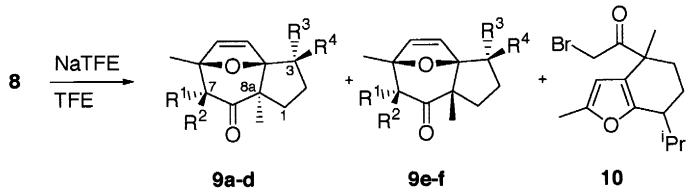
Scheme 2. (a) $(EtO)_2P(=O)CHNaCOOEt$, toluene, reflux, 16 h, 83%; (b) H_2/Pd–C, EtOH, rt, 82%; (c) $LiAlH_4$, Et_2O, reflux, 2 h, 98%; (d) CBr_4, PPh_3, Et_2O, rt, 2 h, 89%; (e) $CH_3CNa(COOEt)_2$, DMF, 100°C, 4 h, 93%; (f) LiCl, H_2O, DMSO, 180°C, 4 h, 81%; (g) CH_2Br_2, LDA, THF, −78°C, 50 min, 88%

For the cycloaddition, the dibromo ketone **8** was reacted in a ca. 0.4 M solution of sodium 2,2,2-trifluoroethoxide (NaTFE) in 2,2,2-trifluoroethanol[14] (TFE) at room temperature. The reaction proceeded very slowly and was finished after 6 days. Unfortunately, the cycloaddition was not stereoselective, and a mixture of six isomers **9a**–**f** (Table 1), together with two diastereomeric furans **10** as byproducts, was obtained (Scheme 3), which was examined by a capillary GC and GC/MS analysis.

Table 1
Reaction of **8** with NaTFE/TFE

product	R^1	R^2	R^3	R^4	yield[a] (%)
9a	Br	H	H	iPr	31 (28)
9b	H	Br	H	iPr	9 (8)
9c	Br	H	iPr	H	14 (14[c])
9d	H	Br	iPr	H	3 (3)
9e	Br	H	H	iPr	25 (21)
9f	Br	H	iPr	H	5[b] (2)
10					11[b] (14)

[a] determined by GC (isolated yields in parentheses).
[b] overlapping signals. [c] contaminated with **9e**.



Scheme 3.

In addition, two other components with the likely molecular formula of $C_{17}H_{23}F_3O_3$, presumably two isomeric unsaturated esters resulting from Favorskii rearrangement[15] of **8** with NaTFE, were detected in traces (ca. 1% each). The cycloadducts **9a**–**f** could be separated by MPLC, the furans **10** were isolated as a mixture.

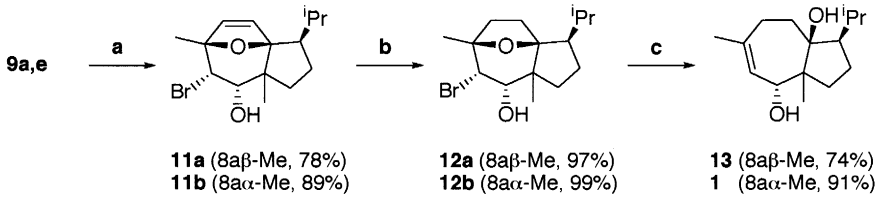
When **9a** was subjected to the basic reaction conditions with NaTFE/TFE at room temperature for 1 week, epimerization occurred at C-7 to give a 3:1 mixture of **9a** and **9b**. Under the same conditions, **9c** yielded a 9:2 mixture of **9c** and **9d** (determined by ^{1}H NMR spectroscopy). Thus, the stereochemistry in **9a** and **9b** differs only at C-7 and the same is true for the epimers **9c** and **9d**.

Due to the carbonyl anisotropy, the ^{1}H NMR signal of an equatorial proton or methyl protons in products obtained by [4+3] cycloaddition appears at higher fields than an axial substituent.[16] The isomers **9a**–**d** exhibited the angular C-8a-methyl groups as singlets at ca. δ 1.0, whilst, for **9e** and **9f** these signals appeared at ca. δ 1.3. From this, one can conclude that the C-8a-methyl groups in **9a**–**d** are orientated equatorial and hence these cycloadducts are *trans*-fused. On the other hand, cycloadducts **9e** and **9f** should exhibit a *cis*-fused carbon framework. This assumption was confirmed by the signals of the carbonyl-C-atoms in the ^{13}C NMR spectra. As in other known *trans*-fused cycloadducts,[4b] these are shifted downfield (ca. 5 ppm) relative to those in the *cis*-fused cycloadducts. The protons at C-7 in **9a** and **9c** resonate at lower fields compared to those in **9b** and **9d**. Therefore, the first should exhibit an equatorial and the latter an axial bromine substituent. For the *cis*-fused cycloadducts **9e** and **9f**, signals for H-7 are found at 4.76 and 4.72 ppm, respectively. These chemical shifts are in good accordance with the values observed for a proton geminal to an equatorial bromine atom in similar constituted bicyclic compounds.[17] X-Ray crystallographic analysis confirmed that the structure of the main isomer is as represented by **9a**.[18] Hence, it follows that **9b** has the same configuration at C-3, whereas **9c** and **9d** should have a β-orientated[19] isopropyl group. To our regret, suitable crystals for X-ray analysis were not obtained for **9e**. But, after inspection of the ^{1}H NMR data[20] of daucol, a quite similar compound, we tentatively postulated an α-orientated isopropyl group in **9e**. This assumption proved correct later by synthesis of lasidiol (vide infra). By-products **10** were characterized by spectroscopic means and GC/MS analysis.

Without doubt, the furans **10** can be regarded as the products of an intramolecular electrophilic substitution. Their occurrence suggested that the cycloadducts **9** are formed by a stepwise mechanism,[21] in which the furan moiety is attacked first in its 2-position by an oxyallyl species. It should be mentioned, that according to quantum chemical calculations[22] the reaction of the hydroxyallyl cation with furan and other 1,3-dienes occurs in a stepwise manner. Oxyallyls generated from **8** could also be present in their highly electrophilic protonated form in the comparatively acidic TFE. As shown above, the cycloadducts **9b** and **9d** with an α-bromo substituent might have been formed at least to some extend by a base-catalyzed epimerization at C-7.

Reduction of cycloadducts **9a** and **9e** with excess lithium aluminum hydride in THF (Scheme 4) proceeded stereoselectively and provided the bromohydrins **11a** and **11b**, both with an axial hydroxy group. Catalytic hydrogenation gave the saturated alcohols **12a** and **12b**. The configuration at C-8 in **11a** and **11b** was established by ^{1}H NMR spectroscopy. In both alcohols, the vicinal coupling constant

between H-7 and H-8 is ca. 5 Hz, the bromohydrins **12a** and **12b** show a slightly smaller value (ca. 4 Hz). The magnitude of this coupling constant served to indicate that the proton at C-8 in the alcohols is α-orientated.[23]



Scheme 4. (a) $LiAlH_4$, THF, rt, 2 h; (b) H_2/Pd–C, MeOH, rt; (c) (1) *n*-BuLi, THF, −78°C; (2) $[C_{10}H_8]Na$, −78 °C, 20 min; (3) H_2O

For the reductive elimination, the alcohols **12a** and **12b** were first deprotonated with an equivalent amount of *n*-butyllithium in THF at −78 °C and then treated with a 0.5 M solution of sodium naphthalenide (1.5 equivalents) in THF at the same temperature. The cleavage of the oxygen-bridge proceeded smoothly within 20 min to furnish **13** and **1** in good yield after aqueous work-up and chromatography. The NMR spectra of our sample of **1** prepared in this manner were in full agreement with that reported for the natural product.[3]

References

1. (a) For a review, see: Gonzáles, A. G.; Barrera, J. B. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Kirby, G. W.; Moore, R. E.; Steglich, W.; Tamm, Ch., Eds.; Springer Verlag: Wien, 1995; Vol. 64, p. 1. (b) Casinovi, C. G.; Cerrini, S.; Motl, O.; Fardella, G.; Fedeli, W.; Gavuzzo, E.; Lamba, D. *Collect. Czech. Chem. Commun.* **1983**, *48*, 2411.
2. (a) Yamasaki, M. *J. Chem. Soc., Chem. Commun.* **1972**, 606. (b) Naegeli, P.; Kaiser, R. *Tetrahedron Lett.* **1972**, *20*, 2013. (c) Audenaert, F.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron* **1987**, *43*, 5593. (d) De Broissia, H.; Levisalles, J.; Rudler, H. *J. Chem. Soc., Chem. Commun.* **1972**, 855. (e) Harayama, T.; Shinkai, Y.; Hashimoto, Y.; Fukushi, H.; Inubushi, Y. *Tetrahedron Lett.* **1983**, *24*, 5241.
3. Wiemer, D. F.; Ales, D. C. *J. Org. Chem.* **1981**, *46*, 5449.
4. (a) Föhlisch, B.; Herter, R. *Chem. Ber.* **1984**, *117*, 2580. (b) Kaiser, R.; Föhlisch, B. *Helv. Chim. Acta* **1990**, *73*, 1504. (c) Harmata, M. *Tetrahedron* **1997**, *53*, 6235.
5. (a) Föhlisch, B.; Kreiselmeier, G., submitted for publication. (b) Kreiselmeier, G. *Dissertation*, Universität Stuttgart, 1998.
6. For a review on ring-opening reactions of oxabicyclic compounds, see: Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.
7. Harmata, M.; Carter, K. W. *Tetrahedron Lett.* **1997**, *38*, 7985.
8. Scholz, S.; Marschall-Weyerstahl, H.; Weyerstahl, P. *Liebigs Ann. Chem.* **1985**, 1935.
9. Cernayová, M.; Kovác, J.; Dandárová, M.; Hasová, B.; Palovcík, R. *Collect. Czech. Chem. Commun.* **1976**, *41*, 764.
10. Johnson, R. L. *J. Med. Chem.* **1984**, *27*, 1351.
11. Petragnani, N.; Yonashiro M. *Synthesis* **1982**, 521.
12. Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen Jr., E. G. E.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.
13. Barluenga, J.; Llavona, L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Perkin Trans 1* **1991**, 297.
14. (a) Föhlisch, B.; Gehrlach, E.; Herter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 137. (b) *Angew. Chem. Suppl.* **1982**, 241.
15. (a) Kende, A. S. *Org. React.* **1960**, *11*, 261. (b) For Favorskii rearrangement in TFE, see: Föhlisch, B.; Gehrlach, E.; Henle, G. *J. Chem. Res. (S)* **1991**, 136. (c) *J. Chem. Res. (M)* **1991**, 1462, and Ref. 5b.
16. Hoffmann, H. M. R.; Clemens, K. E.; Smithers, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 3940.
17. Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1765.
18. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-137334. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax int. code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

19. According to *Chemical Abstracts, Index Guide, Appendix IV*, ¶ 203, I (D), the descriptors α and β are used. The α-side is defined by the oxygen-bridge.
20. Platzer, N.; Goasdoue, N.; Davoust, D. *Magn. Reson. Chem.* **1987**, *25*, 311.
21. Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1.
22. Cramer, C. J.; Barrows, S. E. *J. Org. Chem.* **1998**, *63*, 5523.
23. Treu, J.; Hoffmann, H. M. R. *J. Org. Chem.* **1997**, *62*, 4650.