Pergamon

Tetrahedron Letters 43 (2002) 6351–6353

TETRAHEDRON LETTERS

Straightforward synthesis of the strong ambergris odorant γ-bicyclohomofarnesal and its *endo*-isomer from *R*-(+)-sclareolide

María C. de la Torre,[a,*] Isabel García[a] and Miguel A. Sierra[b]

[a]*Instituto de Química Orgánica, Consejo Superior de Investigaciones Científicas (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain*

[b]*Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain*

Received 19 April 2002; accepted 8 July 2002

Abstract—γ-Bicyclohomofarnesal **1** and its *endo* isomer **5** were prepared in 47 and 26% overall yields, respectively, from commercial *R*-(+)-sclareolide (**7**), in a three-step sequence. The synthetic procedure involves the preparation of Weinreb's amide **9**, dehydration of tertiary alcohol to form compounds **10** and **11**, chromatographic separation and reduction with $LiAlH_4$. This approach is simple and can compete with the syntheses previously reported for the preparation of these important compounds, both in overall yields and in the number of synthetic steps. © 2002 Elsevier Science Ltd. All rights reserved.

γ-Bicyclohomofarnesal (Ambral® **1**) is a strong ambergris odorant with fine tonality.[1] Apart from its value as odorant, aldehyde **1** is a very versatile synthetic intermediate. In fact, it has been converted in a four-step sequence into (−)-Ambrox® (**2**),[2] the commercially more important amber chemical. Additionally, γ-bicyclohomofarnesal (**1**) is a key intermediate in the preparation of other terpene derivatives like (*E*)-dinorlabdadienal **3**[3] and (+)-galanolactone **4**.[4] Furthermore, compound **5**, an isomer of γ-bicyclohomofarnesal (**1**) having an *endo*-double bond, has been prepared recently, and it has been used as the key intermediate in the synthesis of coscinosulfate **6**, a selective inhibitor of Cdc25 protein phosphatase (Fig. 1).[5]

Because of its synthetic and commercial relevance, the synthesis of aldehyde **1** has been repeatedly pursued, and different approaches to this compound are known. With the exception of the synthesis reported by Barrero,[6] who described an efficient entry to γ-bicyclohomofarnesal from (−)-sclareol, the remaining approaches are inefficient linear multistep sequences.[2,7–11]

In clear contrast, there are only two reported syntheses of pure aldehyde **5**. The procedure by Samadi[5] requires 11 steps from *R*-(+)-sclareolide (**7**), while the synthesis by Bockovich[12] was considerably shorter, taking only three steps from the same starting material. During our ongoing project directed towards the synthesis of different types of terpenes,[13] aldehyde **5** was required. To prepare this compound, we followed the procedure

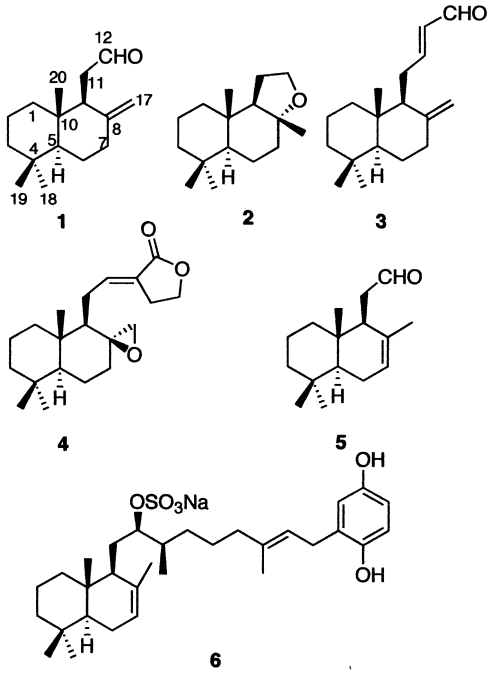
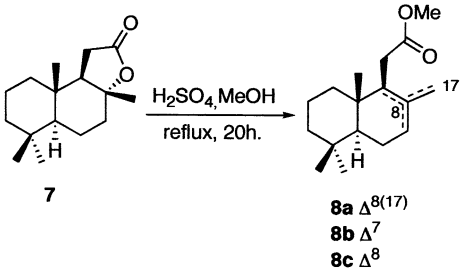


Figure 1.

* Corresponding author. Tel.: +34-915622900; fax: +34-915644853.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01392-8

described by Bockovich,[12] and *R*-(+)-sclareolide (**7**) was submitted to acidic alcoholysis. To our surprise, a mixture of the three possible unsaturated isomers (**8**) was obtained (Eq. (1)). Worse, the mixture was homogeneous on all TLC conditions tested, and we were unable to separate the desired isomer (**8b**). Because all the alternative syntheses of aldehyde **5** proceed through similar mixtures,[11] and the synthesis of Samadi was too long for our purposes, we devised a preparation of aldehydes **1** and **5** using Weinreb's amide **9** derived from *R*-(+)-sclareolide. Reported herein is a three-step synthesis of both γ-bicyclohomofarnesal **1** and its *endo*-isomer **5**, from *R*-(+)-sclareolide (**7**).

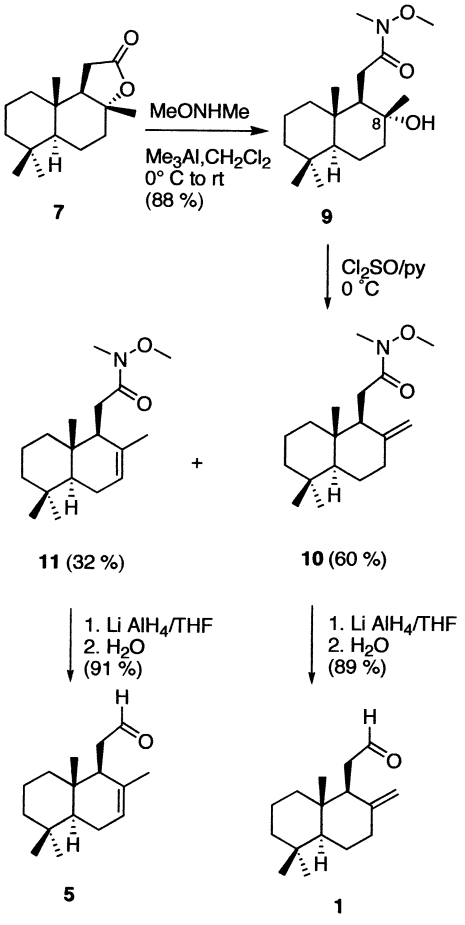


7

8a $\Delta^{8(17)}$
8b Δ^{7}
8c Δ^{8}

(1)

R-(+)-Sclareolide (**7**) was reacted with the dimethylaluminum amide derived from *N*-methoxy-*N*-methylamine yielding the desired Weinreb's amide **9** in 88% yield (Scheme 1).[13,14] The tertiary alcohol of amide **9** was dehydrated in the presence of $SOCl_2$/Py to produce a mixture of $\Delta^{8(17)}$- and Δ^{7}-derivatives (**10** and **11**, respectively). No Δ^{8} isomer was formed in these reaction conditions. The mixture was easily separated by column chromatography to give **10** and **11** in 60 and 32% yields, respectively. These two simple transformations allowed us to access the desired precursors of the target compounds **1** and **5**. In this regard, compound **10** was reacted with $LiAlH_4$ in anhydrous THF to form smoothly the desired γ-bicyclohomofarnesal **1** in a respectable 89% yield.[15] Analogously, when the *endo*-isomer **11** was submitted to $LiAlH_4$ reduction, the desired compound **5** was obtained in 91% yield[16] (Scheme 1).



7 **9**

11 (32 %) **10** (60 %)

5 **1**

Scheme 1.

In conclusion, γ-bicyclohomofarnesal **1** and its *endo* isomer **5** were prepared in 47 and 26% overall yields from commercial *R*-(+)-sclareolide (**7**), in a three-step sequence. This procedure is simple and can compete with the syntheses previously reported for the preparation of these important compounds, both in overall yields and in the number of synthetic steps.

Acknowledgements

Financial support by the Spanish Ministerio de Ciencia y Tecnología (Grant No. BQU2001-1283) is gratefully acknowledged. I. García thanks the MEC (Spain) for a predoctoral fellowship.

References

1. (a) Ohloff, G. *Scent and Fragances*; Springer: Berlin, 1994, p. 218. For selected reviews in fragrance and odorants chemistry, see: (b) Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633; (c) Kraft, P.; Bajgrowicz, J. A.; Denis, C.; Fráter, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2980.
2. Mori, K.; Tamura, H. *Liebigs Ann. Chem.* **1990**, 361.
3. Weyerstahl, P.; Schwieger, R.; Schwope, I.; Hashem, M. A. *Liebigs Ann. Chem.* **1995**, 1389.
4. Nozawa, M.; Ono, E.; Akita, H. *Heterocycles* **2000**, *53*, 1811.
5. Poigny, S.; Nouri, S.; Chiaroni, A.; Guyot, M.; Samadi, M. *J. Org. Chem.* **2001**, *66*, 7263.
6. Barrero, A. F.; Manzaneda, E. A.; Altarejos, J.; Salido, S.; Ramos, J. M.; Simmonds, M. S. J.; Blaney, W. M. *Tetrahedron* **1995**, *51*, 7435.
7. Cambie, R. C.; Clark, G. R.; Goeth, M. E.; Rickard, C. E. F.; Rutledge, P. S.; Ryan, G. R.; Woodgate, P. D. *Aust. J. Chem.* **1989**, *42*, 497.
8. Grant, P. K.; Lai, C.h. K.; Prasad, J. S.; Yap, T. M. *Aust. J. Chem.* **1988**, *41*, 711.
9. Müller, M.; Schroder, J.; Magg, C.; Seifert, K. *Tetrahedron Lett.* **1998**, *39*, 4655.
10. López, J.; Trespalacios, C.; Peña, W.; Cortés, M. *Synth. Commun.* **1992**, *22*, 2599.
11. (a) Sundararaman, P.; Herz, W. *J. Org. Chem.* **1977**, *42*, 806; (b) Cambie, R. C.; Moratti, S. C.; Rutledge, P. S.; Weston, R. J.; Woodgate, P. D. *Aust. J. Chem.* **1990**, *43*, 1151.

12. Cebula, R. E.; Blanchard, J. L.; Boisclair, M. D.; Pal, K.; Bockovich, N. J. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2015.
13. (a) de la Torre, M. C.; Maggio, A.; Rodríguez, B. *Tetrahedron* **2000**, *56*, 8007; (b) de la Torre, M. C.; García, I.; Sierra, M. A. *J. Nat. Prod.* **2002**, *65*, 661–668.
14. Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685.
15. **Preparation of 13,14,15,16-tetranor, 8(17)-labden-12-al (1) from 10**. To a suspension of $LiAlH_4$ (129 mg, 3.4 mmol) in THF (40 mL), under argon and at 0°C, a solution of amide **10** (500 mg, 1.7 mmol) in THF (50 mL) was added drop wise. The mixture was allowed to reach room temperature and it was stirred overnight. The reaction mixture was quenched by adding 100 mL of a 10% w/v KOH solution. The mixture was filtered through Celite®, the organic phase was removed and the aqueous phase was extracted with AcOEt (3×80 mL). The combined organic extracts were dried and concentrated under reduced pressure. The residue was purified over silica gel, using hexanes:AcOEt (49:1) as eluent, to give 350 mg (89%) of pure **1** as a colorless oil: $[\alpha]_D^{22}$ −22.9 (*c* 0.097, $CHCl_3$); IR (neat) ν_{max} 3080, 2929, 2844, 2714, 1725, 1644, 1459, 1388, 1366, 891 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.61 (1H, dd $J=2.38$, 1.47 Hz, CHO), 4.80 (1H, br s, H_B-17), 4.37 (1H, br s, H_A-17), 2.41 (2H, m, 2H-11), 0.88 (3H, s), 0.80 (3H, s), 0.69 (3H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 203.5 (d, C-12), 148.4 (s, C-8), 108.0 (t, C-17), 55.2 (d, C-9), 50.9 (d, C-5), 41.9 (t, C-3), 39.7 (t, C-1)*, 39.3 (t, C-7)*, 38.8 (s, C-10), 37.4 (t, C-11), 33.4 (q+s, C-18+C-4), 24.0 (t, C-6), 21.8 (q, C-19), 19.3 (t, C-2), 14.7 (q, C-20) assignments marked with an asterisk may be interchanged; EIMS *m*/*z* (rel. int.) 235 $[M+1]^+$ (32), 234 $[M]^+$ (5), 205 (7), 190 (29), 177 (15), 153 (11), 137 (100), 123 (49), 121 (30), 109 (47), 95 (56), 81 (54), 69 (48), 55 (34), 41 (38). Anal. C, 81.52; H, 10.75; calcd for $C_{16}H_{26}O$, C, 81.94; H, 11.18%.
16. **Preparation of 13,14,15,16-tetranor-7-labden-12-al (5) from 11**. $LiAlH_4$ (80 mg, 2.1 mmol) was added in portions to a solution of amide **11** (125 mg, 0.42 mmol) in THF (9 mL) at 0°C under argon. The mixture was stirred at this temperature for 30 min until the amide was consumed (TLC analysis). Then, 10 mL of water were added and the reaction mixture was allowed to reach room temperature and was vigorously stirred for 1 h. The reaction mixture was extracted with AcOEt (3×20 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified over silica gel using hexanes:CH_2Cl_2 (17:3) as eluent to give pure **5** as a colorless oil (91 mg, 91%): $[\alpha]_D^{22}$ −29.2 (*c* 0.161, $CHCl_3$); IR (neat) ν_{max} 2924, 2847, 2712, 1725, 1457, 1443, 1387, 1365, 1054, 1022 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.83 (1H, t, $J=2.2$ Hz), 5.45 (1H, br s, H-7), 2.47 (1H, m), 2.35 (2H, m), 1.50 (1H, dd, $J=1.5$, 2.9 Hz), 0.87 (3H, s), 0.86 (3H, s), 0.75 (3H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 203.5 (d, C-12), 132.9 (s, C-8), 123.4 (d, C-7), 49.8 (d, C-9)*, 48.5 (d, C-5)*, 42.3 (t, C-3), 42.0 (t, C-1), 39.5 (t, C-11), 36.0 (s, C-10), 33.1 (q, C-18), 32.9 (s, C-4), 23.6 (t, C-6), 22.5 (q, C-17)*, 21.8 (q, C-19)*, 18.7 (t, C-2), 14.2 (q, C-20) assignments marked with an asterisk may be interchanged; EI MS *m*/*z* (rel. int.) 234 $[M]^+$ (7), 205 (4), 190 (12), 175 (8), 149 (7), 137 (7), 124 (57), 109 (100), 95 (27), 81 (27), 69 (24), 55 (18). Anal. C, 81.65%; H, 10.93%; calcd for $C_{16}H_{26}O$: C, 81.94%; H, 11.18%.