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Tetrahedron Letters 46 (2005) 5321–5324
Tetrahedron Letters

First enantiospecific synthesis of marine nor-sesquiterpene (+)-austrodoral from (−)-sclareol

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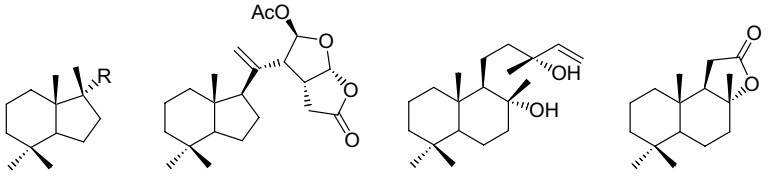
Received 14 April 2005; revised 30 May 2005; accepted 3 June 2005
Available online 21 June 2005

Abstract—A short and efficient synthesis of the rearranged nor-sesquiterpenes (+)-austrodoral (**1**) and (+)-austrodoric acid (**2**), recently isolated from the Antarctic marine mollusk *Austrodoris kerguelenensis*, from diterpene (−)-sclareol (**4**) is reported. The key step of the sequence is the pinacol rearrangement of the drimanetriol **11**.

Marine organisms constitute an inexhaustible source of new natural products exhibiting very different structural patterns and a wide variety of biological activities. Among these, nudibranch mollusks are known to harvest a variety of chemical metabolites, which are involved in the defensive mechanisms of these animals. The study of this chemical defence is an important goal of the research from the ecological point of view and in order to achieve new bioactive compounds.[1]

Recently, Cimino and co-workers, have reported the isolation of (+)-austrodoral (**1**), a nor-sesquiterpene with a new carbon skeleton, from the Antarctic nudibranch *Austrodoric kerguelenensis*.[2] This compound is of great interest due to its structural feature. The unusual rearranged bicyclic moiety, characteristic of some spongian-type diterpenes, such as (+)-norrisolide (**3**),[3] was found in the sesquiterpenes series for the first time. Moreover, the presence of **1** in the skin of the animal seems to be related to some kind of defensive mechanism. On the other hand, the increase of this metabolite in individuals kept in an aquarium for several days suggests a probable role as stress-metabolite.[2]

The scarcity of **1** in its natural source, as well as the observed fast degradation during work-up, have prevented the evaluation of its biological activity, which forces us to develop a suitable synthesis. Very recently, a first synthesis of the related austrodoric acid (**2**) from (+)-sclareolide (**5**) has been reported.[4] Acid **2**, also obtained during the isolation of **1**, is formed by air oxidation of the latter, and is probably a work-up product, as Cimino and co-workers claimed.[2] The reported synthesis of **2**, a possible intermediate to prepare **1**, from **5** (nine steps, 6.8% global yield) involves some low yield transformations and few stereoselective reactions, which makes it a little laborious.



1 R: CHO
2 R: COOH

3 **4** **5**

Keywords: Terpenes; Marine metabolites; Enantiospecific synthesis; Pinacol rearrangement; Triphenylphosphine; Iodine.
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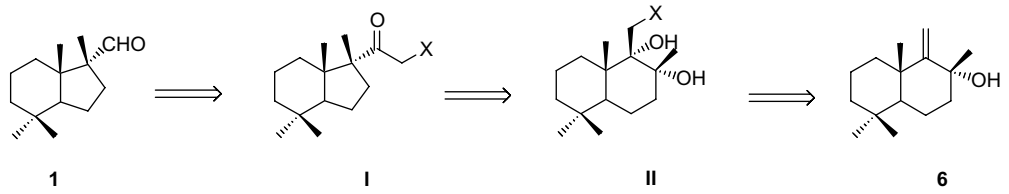
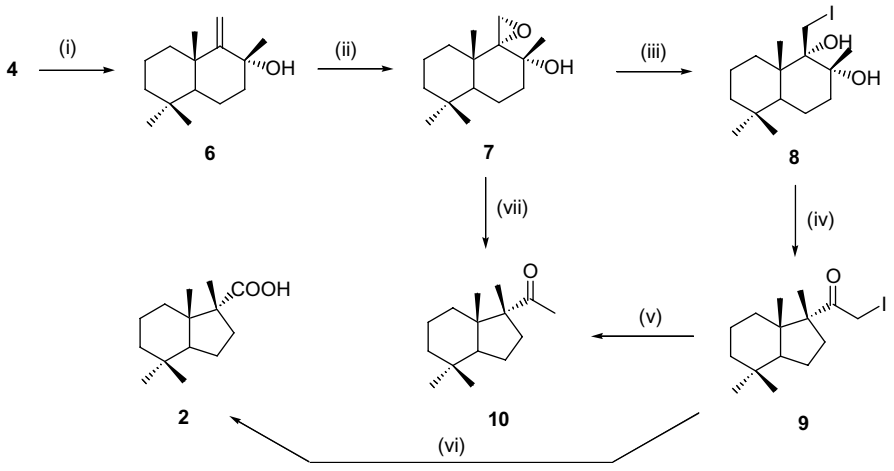
doi:10.1016/j.tetlet.2005.06.010



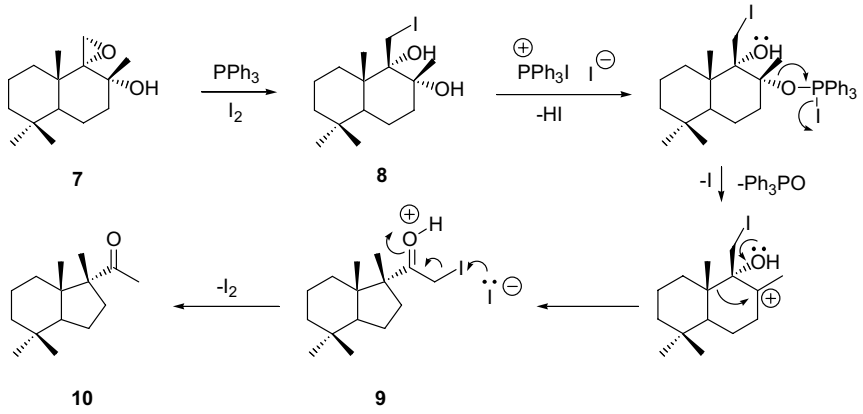
Scheme 1.



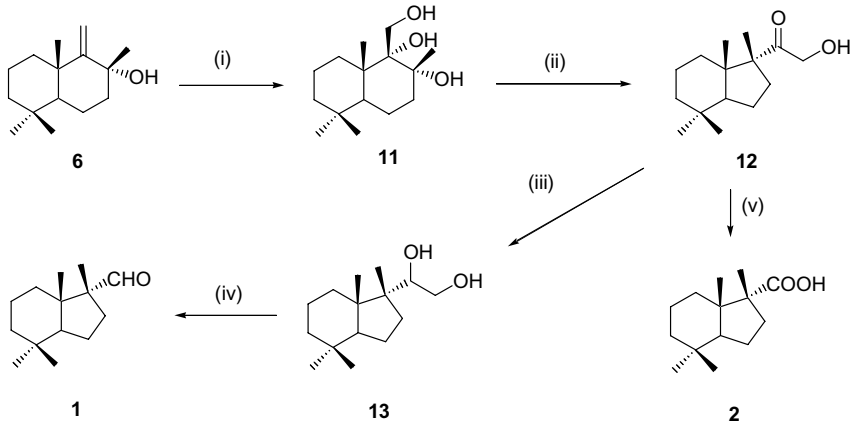
Scheme 2. Reagents and conditions: (i) Ref. 6, four steps, 59%; (ii) MCPBA, CH_2Cl_2, rt, 1 h (quant.); (iii) PPh_3, I_2, CH_2Cl_2, rt, 30 min (quant.); (iv) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 15 min (92%); (v) Ref. 7 (70–85%); (vi) DMSO, reflux, 2 days (30%); (vii) PPh_3, I_2, CH_2Cl_2, rt, 20 min; reflux, 2 h (88%).

Continuing our investigation on the synthesis of bioactive compounds based on homochiral synthons obtained from natural sources, we plan the synthesis of (+)-austrodoral (**1**) from (−)-sclareol (**4**), via 9,11-drimen-8α-ol (**6**)[5] (Scheme 1). Aldehyde **1** will be obtained by degradation of a keto intermediate I, resulting from the pinacol rearrangement of diol II derived from **6**. Obviously, the success of this synthesis will depend strongly on the stereoselectivity for the introduction of the hydroxyl group on C-9.

Scheme 2 shows a first approach to this. The epoxydation of **6** led quantitatively and with complete stereoselectivity to **7**, isolated as a crystalline solid. Epoxyalcohol **7**, which by treatment with different Lewis acids afforded complex mixtures, gave in quantitative yield the crystalline iodohydrin **8**,[8] by reaction with the PPh_3–I_2 system. The treatment of **8** with $BF_3{\cdot}OEt_2$ gave the expected iodoketone **9**[8] in high yield. All attempts at converting **9** into acid **2**, under different haloform reaction conditions were unsuccessful, affording instead methylketone **10**.[8] Compound **9** was converted in low yield into **2** after prolonged reflux in DMSO. It should be emphasized that epoxyde **7** was directly transformed quantitatively into **10**, by treatment with PPh_3 and I_2 in CH_2Cl_2 under reflux. A possible mechanism is depicted in Scheme 3. The pinacol rearrangement of **8** induced by the phosphonium salt, would afford the iodoketone **9**, which would be reduced by iodide anion to give **10**.



Scheme 3.



Scheme 4. Reagents and conditions: (i) OsO_4, H_2O, *t*-BuOH, trimethylamine *N*-oxide, pyridine, reflux, 24 h (87%); (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt, 20 min (95%); (iii) $NaBH_4$, EtOH, rt, 15 min (97%); (iv) $Pb(OAc)_4$, CH_2Cl_2, rt, 45 min (92%); (v) $NaIO_4$, *t*-BuOH–H_2O, reflux, 12 h (91%).

A very efficient transformation of **6** into (+)-austrodoral (**1**), via triol **11**, was achieved (Scheme 4). Compound **11**, which could not be synthesized from **7** by ring opening, was obtained in high yield and with complete stereoselectivity after cis-dihydroxylation of **6**. Treatment of **11** with $BF_3{\cdot}OEt_2$ led to hydroxyketone **12**,[8] a suitable intermediate to prepare **1** and **2**. Reduction of **12** gave diol **13**, which was then easily converted into aldehyde **1**.[8] (+)-Austrodoric acid (**2**)[8] was obtained by treating **12** with $NaIO_4$. It should be remarked that aldehyde **1** is easily transformed into acid **2** by exposition to air of its solutions. This behaviour, also remarked upon by Cimino's group, seems to support the work-up product nature of this acid.

In summary, the first enantiospecific synthesis of marine nor-sesquiterpene (+)-austrodoral (**1**) from (−)-sclareol (**4**) (eight steps, 45% overall yield) is reported. The short synthetic sequence, involving high-yield steps and completely stereoselective processes, makes it possible to prepare large amounts of **1** and thus elaborate bicyclic chiral synthons to gain access to other interesting metabolites, such as **3**.

Acknowledgements

Financial support was received from Ministerio de Ciencia y Tecnología (Project PPQ 2002-03308).

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4. Kultcitki, V.; Ungur, N.; Gavagnin, M.; Carbone, M.; Cimino, G. *Tetrahedron: Asymmetry* **2004**, *15*, 423–428.
5. Alcohol **6** is a natural sesquiterpene isolated from *Aspergillus oryzae*. See: (a) Wada, K.; Tanaka, S.; Marumo, S. *Agric. Biol. Chem.* **1983**, *47*, 1075–1078; (b) Shishido, K.; Omodani, T.; Shibuya, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2285–2287; (c) Dominguez, G.; Hueso-Rodriguez, J. A.; De la Torre, M. C.; Rodriguez, B. *Tetrahedron Lett.* **1991**, *32*, 4765–4768.
6. For syntheses of **6** from **4** see: (a) Alvarez-Manzaneda, E. J.; Chahboun, R.; Barranco Pérez, I.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R. *Org. Lett.* **2005**, *7*, 1477–1480; (b) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; González Díaz, C. *Synlett* **2000**, 1561–1564.
7. Ketone **10** was obtained in 70–85% from **9**, under different haloform reaction conditions, as KI, I_2, KOH, dioxane or NaOBr, NaBr, NaOH, H_2O. See: March, J. A. *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, 5th ed.; Wiley Interscience: New York, 2001; pp 813–814; For recent examples of the use of haloform reaction see: (a) Larionov, O. V.; Kozhushkov, S. I.; de Meijere, A. *Synthesis* **2005**, 158–160; (b) Bolster, M. G.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2002**, *58*, 5275–5285.
8. All new compounds were fully characterized spectroscopically and had satisfactory high resolution mass spectroscopy data. Selected data:
Compound **8**: Crystalline solid, mp: 110 °C (dec). $[\alpha]_D$ +1.1 (0.023 M, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.74 (d, J = 10.7 Hz, 1H), 3.63 (d, J = 10.7 Hz, 1H), 3.16 (s, 1H), 2.54 (br s, 1H), 1.35 (s, 3H), 0.98 (s, 3H), 0.84 (s, 3H), 0.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 75.8 (C), 75.4 (C), 46.2 (CH), 43.7 (C), 41.0 (CH_2), 39.3 (CH_2), 33.8 (CH_2), 33.6 (CH_3), 33.4 (C), 25.4 (CH_3), 21.8 (CH_3), 19.5 (CH_2), 19.4 (CH_2), 17.7(CH_3), 13.4 (CH_2). IR (KBr): 3510, 2945, 2869, 2363, 2337, 1459, 788, 752 cm^{-1}.
Compound **9**: Crystalline solid, mp: 75–77 °C. $[\alpha]_D$ −12.6 (0.012 M, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.03 (d, J = 11.9 Hz, 1H), 3.88 (d, J = 11.9 Hz, 1H), 2.29 (m, 1H), 1.32 (s, 3H), 0.88 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.6 (C), 62.5 (C), 52.5 (CH), 47.1 (C), 40.9 (CH_2), 36.1 (CH_2), 33.7 (CH_3), 33.4 (C), 33.3 (CH_2), 21.7 (CH_2), 21.5 (CH_3), 21.1 (CH_3), 20.0 (CH_2), 15.6 (CH_3), 8.3 (CH_2). IR (KBr): 2945, 2869, 2363, 2337, 1693, 1459, 788, 752 cm^{-1}.
Compound **10**: $[\alpha]_D$ −1.1 (0.028 M, $CHCl_3$). ^1H NMR($CDCl_3$, 400 MHz): δ 2.15 (m, 1H), 2.04 (s, 3H), 1.13 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H), 0.79 (s, 3H). ^{13}C NMR

($CDCl_3$, 100 MHz): δ 215.2 (C), 61.7 (C), 52.4 (CH), 46.7 (C), 41.0 (CH_2), 35.9 (CH_2), 33.7 (CH_3), 33.2 (C), 32.5 (CH_2), 29.5 (CH_3), 21.7 (CH_2), 21.5 (CH_3), 20.8 (CH_3), 20.1 (CH_2), 15.9 (CH_3). IR: 2929, 1694, 1465, 1234, 793, 741 cm^{-1}.

Compound **12**: $[\alpha]_D$ −9.1 (0.032 M, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.27 (d, J = 18.5 Hz, 1H), 4.18 (d,J = 18.5 Hz, 1H), 3.71 (br s, 1H), 2.20 (m, 1H), 1.12 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H), 0.84 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 216.4 (C), 67.4 (CH_2), 59.2 (C), 52.4 (CH), 47.7 (C), 40.8 (CH_2), 35.4 (CH_2), 33.8 (CH_3), 33.1 (CH_2), 30.8 (C), 21.9 (CH_2), 21.5 (CH_3), 19.9 (CH_2), 18.4 (CH_3), 16.1 (CH_3). IR (film): 3479, 2928, 1693, 1465, 1383, 996, 794, 752 cm^{-1}.

(+)-Austrodoric acid (**2**): Crystalline solid, mp: 172–173 °C. $[\alpha]_D$ +4.4 (0.054 M, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 184.4 (C), 56.6 (C), 53.4 (CH), 46.7 (C), 41.3 (CH_2), 35.3 (CH_2), 33.8 (CH_3), 33.2 (C), 33.0 (CH_2), 21.7 (CH_2), 21.6 (CH_3), 20.5 (CH_3), 20.1 (CH_2), 15.7 (CH_3). IR (KBr): 3300–2800, 2948, 2929, 1686, 1462, 772 cm^1.

(+)-Austrodoral (**1**): ^1H and ^{13}C NMR data are identical to those reported in the literature.[2] $[\alpha]_D$ +9.0 (0.022 M, $CHCl_3$). IR (film): 2948, 2868, 1693, 1462, 1374 cm^1.