Pergamon

Tetrahedron Letters 39 (1998) 741–744

TETRAHEDRON LETTERS

Concise Total Synthesis of (±)-Palominol and (±)-Dolabellatrienone via a Dianion-Accelerated Oxy-Cope Rearrangement

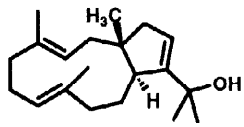
E. J. Corey* and Robert S. Kania

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

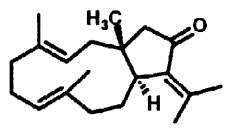
Received 23 September 1997; accepted 7 November 1997

Summary: *A short synthesis of (±)-palominol (**1**) and (±)-dolabellatrienone (**2**) starting from farnesol is reported. Noteworthy steps include an intramolecular pinacol coupling to form a 15-membered carbocyclic diol and subsequent dianion-accelerated oxy-Cope rearrangement to form the 11,5-trans-fused ring system of the dolabellanes.*

Palominol (**1**) and dolabellatrienone (**2**) are naturally occurring members[1] of the widely distributed dolabellane class of marine diterpenoids[1c, 2] which is characterized by the unusual *trans*-bicyclo[9.3.0]tetradecane nucleus. Most dolabellanes exhibit antimicrobial activity, and some possess antitumor activity. For example, **1** displays cytotoxicity (IC_{50} = 10 μg/mL) toward the human colon (HCT 116) cell line.[3] Recently, three syntheses of naturally occuring dolabellanes have been reported[4] and general methods of constructing the bicyclo[9.3.0]tetradecane nucleus have also been described.[5] We previously reported the first enantioselective synthesis of a naturally occurring dolabellane, dolabellatrienone (**2**), via a diazaborolidine-mediated asymmetric Claisen rearrangement.[4a, 6] We have employed a related [3,3]-sigmatropic oxy-Cope rearrangement for the rapid construction of (±)-**1** and (±)-**2** as described herein.



Palominol (1)

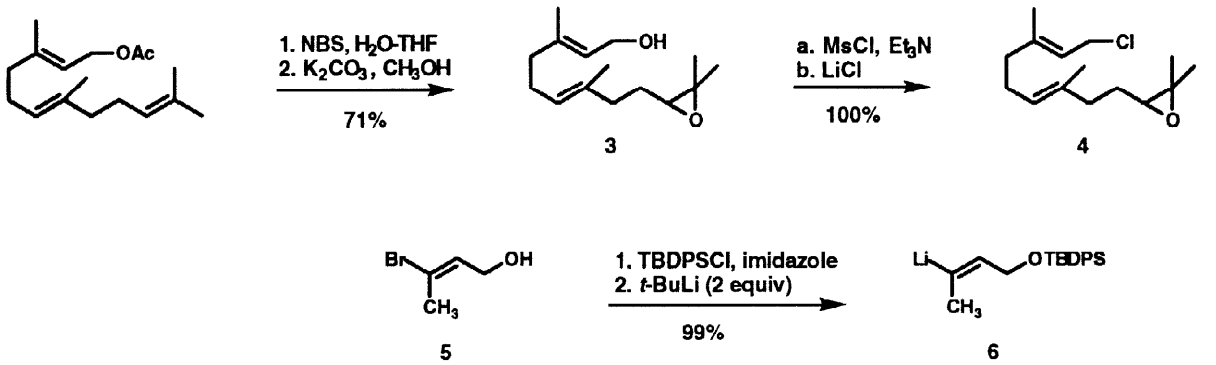


Dolabellatrienone (2)

In the initial stage of the synthesis, intermediates **4** and **6** were prepared for subsequent coupling as illustrated in Scheme 1. Farnesol acetate was treated with 1.1 equiv of *N*-bromosuccinimide (THF-H_2O, 0 °C, 2 h) to achieve position selective bromohydrin formation and subsequently with 2.5 equiv of K_2CO_3-CH_3OH (23 °C, 2 h) to effect methanolysis of the ester and ring closure to form epoxide **3** (71%). Reaction of **3** with 1.2 equiv of methanesulfonyl chloride (Et_3N, CH_2Cl_2, -40 °C, 30 min) followed by addition of 10 equiv of LiCl in THF and warming to 0 °C for 2 h afforded allylic chloride **4** (100%). Bromo alcohol **5**[7] was treated with 1.2 equiv of *t*-butyldiphenylsilyl chloride (1.5 equiv of imidazole, DMF, 23 °C, 30 min) to form the

0040-4039/98/$19.00
PII: S0040-4039(97)10614-1

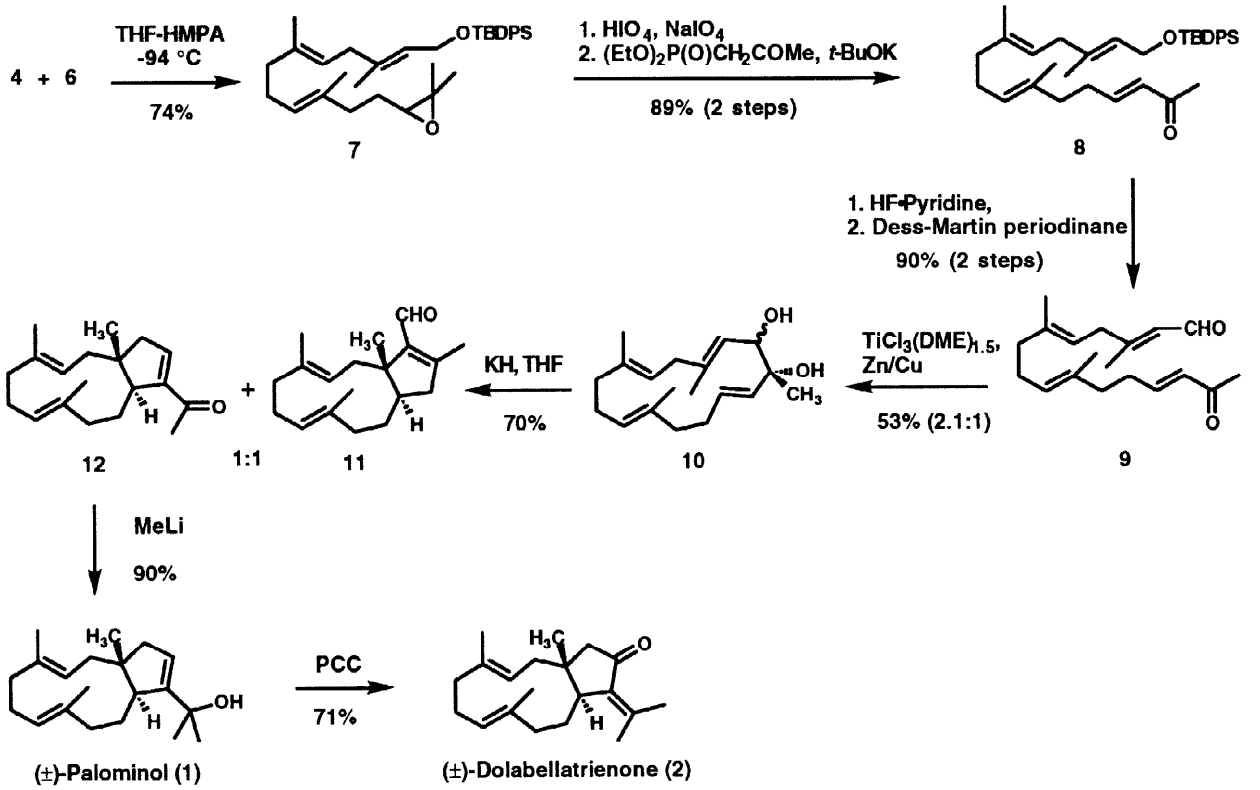
Scheme 1. Synthesis of Coupling Partners **4** and **6**



corresponding silyl ether (99%). Lithium-halogen exchange (2 equiv of *t*-butyllithium, THF, -40 °C, 30 min) afforded the lithium reagent **6** which was used immediately.

The convergent preparation of the pinacol cyclization substrate **9** from building blocks **4** and **6** was accomplished in 5 steps as shown in Scheme 2. Addition of allylic chloride **4** to a solution of lithium reagent **6** (2 equiv, THF-HMPA, -94 °C, 30 min) afforded triene **7** (74%). The epoxide was cleaved with acidic periodate (1.7 equiv, THF-H_2O, 23 °C, 50 min) to afford the corresponding aldehyde which underwent olefination (5 equiv of $(EtO)_2P(O)CH_2COCH_3$, 4.5 equiv of *t*-BuOK, THF, -20 °C, 3 h) to produce enone **8** (89%, 2 steps).

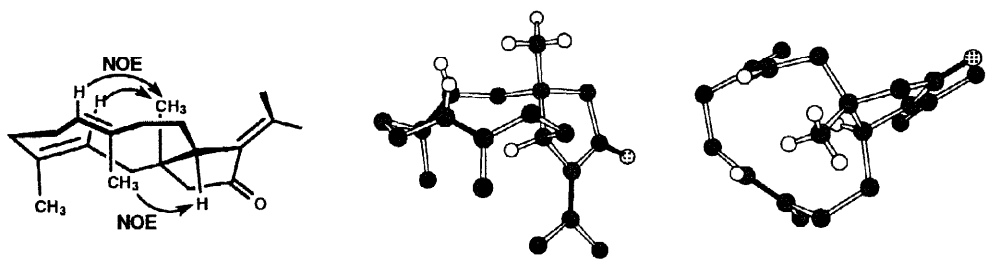
Scheme 2. The Total Synthesis of (±)-Palominol and (±)-Dolabellatrienone



Desilylation (4 equiv of HF•pyridine, THF, 23 °C, 3 h) was followed by Dess-Martin oxidation[8] (1.5 equiv of periodinane, CH_2Cl_2, 23 °C, 30 min) to give the cyclization substrate **9** (90%, 2 steps). Pinacol cyclization was carried out by slow addition of **9** to low valent titanium (7 equiv of $TiCl_3$-$DME_{1.5}$, 30 equiv of Cu/Zn, 0.01 M in DME, -50 to -55 °C, 32 h addition, then 14 h) to provide a separable mixture of diols (2.1:1, 53%).[9] The predominant diol underwent dianion-accelerated oxy-Cope rearrangement (5 equiv of KH, THF, 45 °C, 1.5 h) followed by spontaneous aldol condensation to give a 1:1 mixture of products with *trans*-11,5-fused ring systems, **11** and **12** (70% total). The bicyclic ketone **12** was treated with 5 equiv of methyllithium (Et_2O, -20 °C, 2.5 h) to afford (±)-palominol (**1**) in 90% yield.[10] Synthetic palominol was oxidized with 5 equiv of pyridinium chlorochromate[11] (CH_2Cl_2, 23 °C, 1.5 h) to give (±)-dolabellatrienone (**2**) (71%).[12]

This synthesis of racemic **2** has made possible the determination of the preferred conformation. Unlike enantiopure **2**, which is an oil, the racemate is a crystalline solid (mp 87-89 °C). The solid-state conformation of (±)-**2** was determined by single crystal X-ray diffraction analysis to be as shown in Figure 1. The two rings of dolabellatrienone are not approximately coplanar, as has been proposed for the solution conformation based on NMR studies,[1b] but instead, nearly orthogonal (Figure 1). This conformation demonstrated for crystalline **2** is consistent with the previously observed NOE enhancements,[1b] and hence could also be a preferred conformation in solution.[13, 14]

Figure 1. Comparison of NMR-Based Conformation and X-Ray Structure of Dolabellatrienone



The synthesis described herein provides (±)-**1** in 11 steps (5.3% overall) and (±)-**2** in 12 steps (3.8% overall) from farnesol acetate and demonstrates for the first time that an anion-accelerated oxy-Cope rearrangement can produce strained medium ring compounds from larger, less strained carbocycles, which can be generated readily by reductive pinacol coupling.

References and Notes

1. (a) Look, S. A.; Fenical, W. *J. Org. Chem.* **1982**, *47*, 4129. (b) Shin, J.; Fenical, W. *J. Org. Chem.* **1991**, *56*, 3392. (c) For a recent review of natural dolabellane marine diterpenoids, see: Rodriques, A. D. *Tetrahedron* **1995**, *51*, 4571.
2. For original literature on other members of the dolabellane family, see: (a) Ireland, C.; Faulkner, D. J.; Finer, J.; Clardy, J. *J. Am. Chem. Soc.* **1976**, *98*, 4664. (b) Tringali, C.; Piatelli, M.; Nicolosi, G. *Tetrahedron* **1984**, *40*, 799. (c) Rao, C. B.; Pullaiah, K. C.; Surapeneni, R. K.; Sullivan, B. W.; Albizati, K. F.; Faulkner, D. J.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 2736. (d) Matsuo, A.; Yoshida, K.; Uohama, K.; Hayashi, S.; Connolly, J. D.; Sim, G. A. *Chem. Lett.* **1985**, 935. (e) González, A. G.; Martín, J. D.; Norte, M.; Pérez, R.; Weyler, V.; Rafii, S.; Clardy, J. *Tetrahedron Lett.* **1983**, *24*, 1075. (f) Mori, K.; Iguchi, K.; Yamada, N.; Yamada, Y.; Inouye, Y. *Tetrahedron Lett.* **1987**, *28*, 5673. (g) Kobayashi, M.; Son, B. W.; Fujiwara, T.; Kyogoku, Y.; Kitagawa, I. *Tetrahedron Lett.* **1984**, *25*, 5543.
3. Rodriquez, A. D.; Acosta, A. L.; Dhasmana, H. *J. Nat. Prod.* **1993**, *56*, 1843.
4. (a) Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 1229. (b) Williams, D. R.; Coleman, P. J. *Tetrahedron Lett.* **1995**, *36*, 35. (c) Jenny, L.; Borschberg, H.-J. *Helv. Chim. Acta.* **1995**, *78*, 715.
5. (a) Williams, D. R.; Coleman, P. J.; Henry, S. S. *J. Am. Chem. Soc.* **1993**, *115*, 11654. (b) Williams, D. R.; Coleman, P. J.; Nevill, C. R.; Robinson, L. A. *Tetrahedron Lett.* **1993**, *34*, 7895. (c) Mehta, G.; Karra, S. R.; Krishnamurthy, N. *Tetrahedron Lett.* **1994**, *35*, 2761. (d) Kato, N.; Higo, A.; Nakanishi, K.; Wu, X.; Takeshita, H. *Chem. Lett.* **1994**, 1967. (e) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1996**, *37*, 7661.
6. For a detailed study of this diazaborolidine-mediated Claisen rearrangement methodology, see: (a) Corey, E. J.; Lee, D-Y. *J. Am. Chem. Soc.* **1991**, *113*, 4026. For its application in the synthesis of fuscol, see: (b) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193.
7. Bromo alcohol **5** was made according to Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, *12*, 1051.
8. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. For an improved preparation of Dess-Martin periodinane, see: (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
9. Relative stereochemistry was not assigned for these intermediates. For pinacol coupling with low valent titanium, see: (a) McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169. (b) McMurry, J. E.; Rico, J. G.; Shih, Y. *Tetrahedron Lett.* **1989**, *30*, 1173. (c) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942. (d) McMurry, J. E.; Siemers, N. O. *Tetrahedron Lett.* **1993**, *34*, 7891.
10. The ^{1}H and ^{13}C NMR, IR and MS obtained for synthetic **1** were identical to those recorded previously. For data, see: Caceres, J.; Rivera, M. E.; Rodriguez, A. D. *Tetrahedron* **1990**, *46*, 3422. For corrected structure, see: Shin, J.; Fenical, W. *J. Org. Chem.* **1991**, *56*, 3392.
11. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647. For oxidation of tertiary allylic alcohols, see: Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
12. The ^{1}H NMR, ^{13}C NMR, UV, IR and MS data obtained for synthetic **2** were identical with those obtained for natural dolabellatrienone. We are grateful to Dr. William Fenical for providing copies of the spectra of natural **2**.
13. The X-ray crystal diffraction analysis was performed by Dr. Mark C. Noe. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

14. This research was generously supported by the National Science Foundation and the National Institutes of Health.