Total Synthesis of the Diterpenoid (±)-Ambliol B

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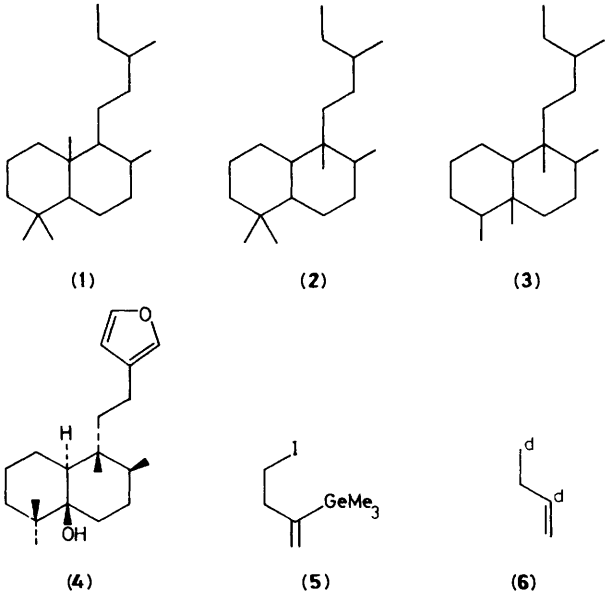
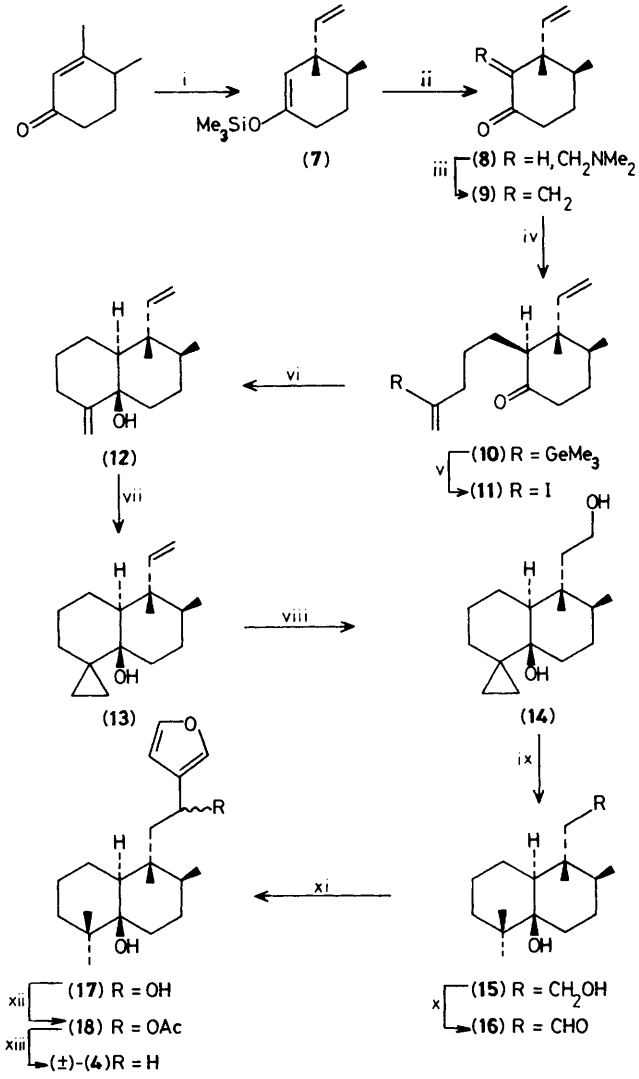
The diterpenoid (±)-ambliol B (**4**) has been derived synthetically from 3,4-dimethylcyclohex-2-en-1-one *via* a 13-step sequence of reactions.

It is highly likely that the clerodane diterpenoids [general carbon skeleton (**3**)] are biogenetically derived from the labdanes [carbon skeleton (**1**)].[1] Thus, while (**1**) retains the 'original' isoprenoid arrangement present in geranylgeranyl diphosphate, (**3**) can be formally obtained from (**1**) *via* a series of 1,2-shifts. Interestingly, there are a (small) number of diterpenoids[2—5] that possess a carbon framework (**2**) which, in terms of biogenetic rearrangement, lies between the labdane (**1**) and clerodane (**3**) skeletons. One such natural product, (−)-ambliol B, was isolated[2] from the marine sponge *Dysidea amblia* and was recently shown[3] to possess the constitution and relative stereochemistry indicated in (**4**). From a synthetic viewpoint, the fact that (**4**) contains a tertiary, angular hydroxy group adjacent to a quaternary centre is particularly noteworthy. We report here a relatively short total synthesis of (±)-(**4**) *via* a route in which a key step involves the use of a new cuprate reagent derived from 4-iodo-2-(trimethylgermyl)but-1-ene (**5**). Overall, in this synthesis, (**5**) performs as a synthetic equivalent to the but-1-ene d^2,d^4-synthon (**6**).[6]

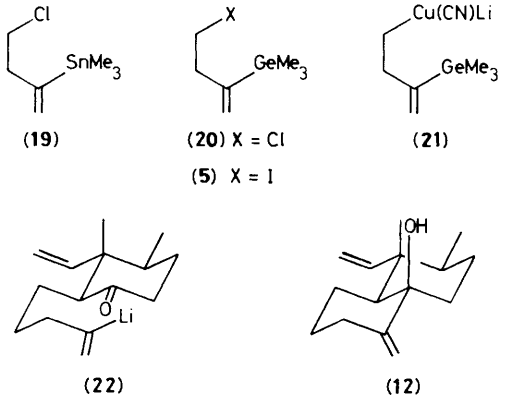
A copper(I)-catalysed reaction of 3,4-dimethylcyclohex-2-en-1-one[7] with vinylmagnesium bromide in the presence of Me_3SiCl[8] gave the enol silyl ether (**7**) (see Scheme 1).† As expected,[9] the reaction was highly stereoselective. Although (**7**) is readily converted into the corresponding lithium enolate, treatment of the latter species with a primary alkyl iodide does not result in alkylation at the carbon adjacent to the quaternary centre. However, reaction[10] of the enolate anion derived from (**7**) with *N,N*-dimethyl(methylene)ammonium iodide provided the keto amine (**8**), which, upon treatment with *m*-chloroperoxybenzoic acid in CH_2Cl_2, followed by direct elution of the resultant reaction mixture through a column of silica gel, afforded the *very unstable*





Scheme 1. *Reagents and conditions:* i, CH_2=$CHMgBr$ (1.5 equiv.), $CuBr{\cdot}Me_2S$ (5 mol %), Me_3SiCl (2 equiv.), hexamethylphosphoramide (2.4 equiv.), tetrahydrofuran (THF), −78 °C, 90%; ii, MeLi, THF, 0 °C → room temp.; $[Me_2N{=}CH_2]I$ (2 equiv.), −78 °C → room temp., 84%; iii, *m*-chloroperoxybenzoic acid, CH_2Cl_2, room temp., 15 min, 76%; iv, (**21**) (2 equiv.), Me_3SiCl (2 equiv.), THF, −78 °C; NH_4Cl, H_2O; v, I_2, CH_2Cl_2, room temp., overnight, 42% from (**9**); vi, Bu^nLi (2 equiv.), THF, −78 °C, 10 min, 88%; vii, CH_2I_2 (3 equiv.), Et_2Zn (2.4 equiv.), air, PhH, 0 °C, 30 min, 91%; viii, BH_3, THF, room temp.; H_2O_2, NaOH, H_2O, 73%; ix, H_2 (1.5 atm.), Pt, HOAc, room temp., 55 min, 87%; x, $C_5H_5N{\cdot}CrO_3{\cdot}HCl$, NaOAc, CH_2Cl_2; xi, 3-lithiofuran, Et_2O, −70 °C → room temp.; xii, Ac_2O, C_5H_5N, CH_2Cl_2, 42% from (**15**); xiii, Li, NH_3, THF, −78 °C, 15 min, 76%.

† The substances (**7**), (**10**)—(**15**), (**18**), and (±)-(**4**) (Scheme 1) were carefully purified, exhibitied spectra in full accord with assigned structures, and gave satisfactory results in molecular mass determinations (high resolution mass spectrometry). Compounds (**9**) and (**16**) are very unstable and were used immediately after their preparation. The keto amine (**8**) and the diol (**17**) showed the expected spectral characteristics, but were not rigorously purified.



(19) (20) X = Cl (5) X = I (21) (22) (12)

enone (**9**). It was necessary to use this material immediately after its preparation.

4-Chloro-2-lithiobut-1-ene, obtained by transmetallation [MeLi, tetrahydrofuran (THF), −78 °C] of the stannane (**19**),[11] reacted smoothly with Me_3GeBr at −78 °C to afford 4-chloro-2-(trimethylgermyl)but-1-ene (**20**), which was readily converted (NaI, acetone, reflux) into the iodide (**5**) [72% from (**19**)]. Treatment of (**5**) with Bu^tLi (2 equiv., THF, −95 °C), followed by addition of CuCN, provided a solution of the lower order heterocuprate (**21**).‡

Reaction of the enone (**9**) with the cuprate (**21**) in the presence of Me_3SiCl gave, after treatment of the resultant solution with aqueous NH_4Cl, the keto trimethylgermane (**10**). Since, on the basis of conformational analysis, (**10**) would be expected to be considerably more stable than its C-2 epimer, the stereochemistry of this substance was readily assigned. Treatment of (**10**) with iodine in CH_2Cl_2 produced, slowly, the key keto iodide (**11**).

Cyclisation of (**11**) by reaction of this material with Bu^nLi in cold THF[12] gave a single, *trans*-fused product (**12**) in high yield. This process would be anticipated to occur *via* an intermediate possessing the conformation (**22**), with intramolecular attack of the vinyl-lithium moiety on the equatorial face of the cyclohexanone carbonyl group. Consequently, the highly stereoselective formation of (**12**) was not unexpected.

Chemoselective cyclopropanation[13] of the diene (**12**) under carefully defined conditions afforded (**13**), which was readily transformed into the diol (**14**). Interestingly, hydrogenolysis of the cyclopropane ring in (**14**) occurred under conditions much milder than those normally required for this type of reaction. Oxidation of the resultant diol (**15**) gave the unstable aldehyde (**16**), which was immediately treated with 3-lithio furan[14] in Et_2O. The derived alcohol (**17**) was converted into the acetate (**18**), which, upon *brief* treatment with excess lithium in NH_3–THF at −78 °C, gave (±)-ambliol B (**4**), an oil that exhibited δ_H (400 MHz, $CDCl_3$) 0.84 (d, 3H, *J* 6.5 Hz), 0.86, 0.87, 1.00 (s, s, s, 3H each), 1.12 (br. d, 1H, *J* 13 Hz), 1.18 (s, 1H, OH), 1.29—1.73 (diffuse m, 13H), 2.26 (td, 1H, *J* 14, 5.3 Hz), 2.36 (td, 1H, *J* 14, 5.0 Hz), 6.28 (br. s, 1 H), 7.22 (br. s, 1H), 7.35 (t, 1H *J* 1.5 Hz); δ_C (75 MHz, C_6D_6) 16.2, 17.7, 18.5, 21.9, 22.5, 24.1, 24.7, 26.7, 32.4, 36.7, 37.1, 38.2, 39.0, 39.1, 41.2, 75.9, 111.3, 125.9, 138.8, 143.0. The spectra of our synthetic (±)-(**4**) were identical with those of natural (−)-ambliol B.

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‡ Attempts to prepare, *via* similar chemistry, a structurally analogous cyanocuprate from 4-iodo-2-(trimethylstannyl)but-1-ene failed.

References

1 M. H. Beale and J. MacMillan, *Nat. Prod. Rep.*, 1988, **5**, 247.
2 R. P. Walker and D. J. Faulkner, *J. Org. Chem.*, 1981, **46**, 1098.
3 R. P. Walker, R. M. Rosser, D. J. Faulkner, L. S. Bass, H. Cun-heng, and J. Clardy, *J. Org. Chem.*, 1984, **49**, 5160.
4 T. Nakatsu, D. J. Faulkner, G. K. Matsumoto, and J. Clardy, *Tetrahedron Lett.*, 1984, **25**, 935.
5 R. Fathi-Afshar and T. M. Allen, *Can. J. Chem.*, 1988, **66**, 45.
6 *Cf.* D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 239.
7 A. Pons, J.-C. Milhavet, and J.-P. Chapat, *Bull. Soc. Chim. Fr.*, 1979, **7—8** (Pt. 2), 381.
8 Y. Horiguchi, S. Matsuzawa, E. Nakamura, and I. Kuwajima, *Tetrahedron Lett.*, 1986, **27**, 4025.
9 F. E. Ziegler, G. R. Reid, W. L. Studt, and P. A. Wender, *J. Org. Chem.*, 1977, **42**, 1991.
10 S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, 1976, **98**, 6715.
11 E. Piers and V. Karunaratne, *Tetrahedron*, 1989, **45**, 1089.
12 E. Piers and P. C. Marais, *Tetrahedron Lett.*, 1988, **29**, 4053.
13 J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, 1968, **24**, 53; S. Miyano and H. Hashimoto, *J. Chem. Soc., Chem. Commun.*, 1971, 1418.
14 Y. Fukuyama, Y. Kawashima, T. Miwa, and T. Tokoroyama, *Synthesis*, 1974, 443.