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Enantiospecific synthesis of (+)-herbertene

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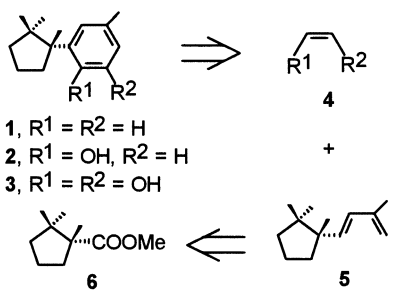
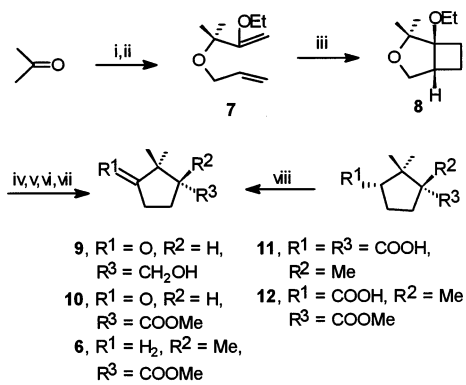
Abstract—A total synthesis of (+)-herbertene from (+)-camphoric acid is described using a Diels–Alder reaction as the key step.

Herbertanes belong to an expanding family[1] of sesquiterpenes possessing a 3-methyl-(1,2,2-trimethylcyclopentyl) cyclohexane skeleton. Herbertene **1**, herbertenol **2** and herbertene diol **3** are a few representative examples. In recent years, herbertanes have become popular synthetic targets[2], as some members of this family exhibit a wide range of biological activities, such as antifungal, neurotrophic and *anti*-lipid peroxidation. The synthesis of these compounds is associated with the difficulty in the generation of two adjacent quaternary centers on a cyclopentane ring and a highly substituted aromatic ring. We have recently developed a general strategy for the synthesis of these compounds. The present strategy[3], involving construction of the vicinally substituted cyclopentane ring followed by elaboration of one of the substituents to an aromatic ring, differs from conventional approaches[2,4] of annulating the cyclopentane ring at the benzylic center of a properly substituted aromatic ring. The key concept in our strategy is the generation of the six-membered ring through a Diels–Alder reaction of the dienophile **4** with the diene **5** prepared from the preformed cyclopentane derivative **6**. Thus, a proper choice of the dienophile **4** will lead to the herbertanes **1**, **2** or **3**. To demonstrate the feasibility of this protocol, we herein report a total synthesis of (+)-herbertene. To date there have only been two reports[3a,c] on the synthesis of the natural enantiomer (−)-herbertene. However, (+)-herbertene has not yet been synthesized.



The sterically congested cyclopentane derivative **6** was obtained through two different routes. The first route begins with the cyclopentane derivative **10**, which was previously prepared[5] by us and used as an intermediate for the total synthesis[6] of a cyclopentanoid natural product. Compound **10** was prepared from acetone as delineated in Scheme 1. The keto-ester **10** was then transformed to the ester **6**[7] in two steps through a Huang–Minlon reduction of the carbonyl group fol-



Scheme 1. *Reagents and conditions*: (i) ethyl vinyl ether, *t*-BuLi, THF, 81%; (ii) NaH, THF, allyl bromide, HMPA, 73%; (iii) hν, CuOTf, Et_2O, 88%; (iv) TfOH, CH_2Cl_2, 84%; (v) Jones oxidation then CH_2N_2; (vi) $N_2H_4{\cdot}H_2O$, $N_2H_4{\cdot}HCl$, KOH, digol, 200°C then MeOH, H_2SO_4, 41%; (vii) LDA, THF, HMPA, MeI, 77%; (viii) (a) MeOH, H_2SO_4, 92%; (b) MeOH, KOH, 89%; (c) *hv*, *t*-BuSH, quinoline, C_6H_6, 59%.

Keywords: aromatization; decarboxylation; Diels–Alder reaction; terpenoids.

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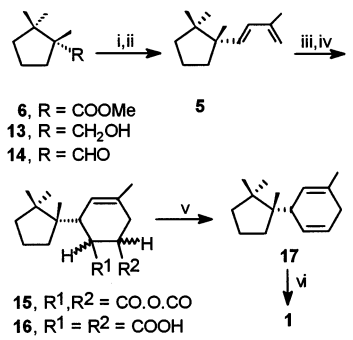
lowed by methylation (LDA-MeI), anticipating that either the ester **6** or the alcohol **13** could be resolved using enzymes to provide access to both enantiomers. In the second route, camphoric acid **11**, through its dimethyl ester, was converted to the monomethyl ester **12** by selective hydrolysis of the secondary ester functionality. Photo-induced decarboxylation[8] of the acid **12** then afforded the ester **6**.

After successfully establishing the desired adjacent quaternary centers on the cyclopentane ring, attention was given to the construction of the aromatic ring. Toward this end, the ester **6** was reduced with lithium aluminum hydride and the resulting alcohol **13** was oxidized to afford the aldehyde **14** (Scheme 2). Wittig olefination of the aldehyde **14** with the ylide generated from methallyl triphenyl phosphonium chloride with *n*-BuLi afforded the diene **5** in 46% yield. The Diels–Alder reaction was carried out by heating a solution of the diene **5** and maleic anhydride in toluene at 80°C to afford the adduct **15** as an inseparable mixture of two diastereoisomers in a 1:2 ratio. Attempted chromatographic purification of the crude product caused hydrolysis of the anhydride functionality leading to the isolation of the anhydrides **15** and the corresponding dicarboxylic acids **16** in 63 and 18% yields, respectively. As the cyclohexene ring needs to be aromatized for completion of the synthesis, the mixture of the Diels–Alder adducts, without further purification, was used directly for the subsequent steps.

Hydrolysis of the anhydride mixture afforded the dicarboxylic acids **16**, mp 117–119°C. The mixture of the dicarboxylic acids thus obtained was then subjected to decarboxylation. The conventional decarboxylation procedure involving $Pb(OAc)_4$ gave a poor yield (25%) of the diene **17** along with herbertene **1**. However, photodecarboxylation[8] afforded the diene **17** in reasonably good yield (40%). Aromatization of the cyclohexadiene derivative **17** was then effected by heating its benzene solution at 60°C with DDQ to afford herbertene **1** in 70% yield. The ^1H and ^{13}C NMR spectroscopic data of this sample were found to be identical



Scheme 2. *Reagents and conditions*: (i) (a) $LiAlH_4$, Et_2O, 84%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 89%; (ii) $H_2C{:}C(Me)\text{-}CH_2PPh_3{}^+Cl^-$, *n*-BuLi, Et_2O, 46%; (iii) maleic anhydride, $C_6H_5CH_3$, 80°C, 63%; (iv) NaOH, H_2O, EtOH, 94%; (v) *hv*, acridine, C_6H_6, 40%; (vi) DDQ, C_6H_6, 60°C, 70%.

with those reported in literature.[3a] Thus, starting with more readily available (+)-camphoric acid, (+)-herbertene,[9] $[\alpha]_D^{30} = +56.85$ (*c* 0.54, $CHCl_3$) was obtained. As (−)-camphoric acid is also commercially available, the present route also provides access to the natural herbertanes.

Acknowledgements

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References

1. Connolly, J. D.; Hill, R. A. In *Dictionary of Terpenoids*, 1st ed.; Chapman and Hall: London, 1991; Vol. 1, pp. 299–300. Also see: Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 217–241; **1993**, *10*, 397–419; **1994**, *11*, 533–554; **1995**, *12*, 303–320; **1996**, *13*, 307–326; **1997**, *14*, 145–162; **1998**, *15*, 73–92.
2. Srikrishna, A.; Rao, M. S. *Tetrahedron Lett.* **2001**, *42*, 5781–5782 and references cited therein.
3. This type of approach has recently been reported for the synthesis of herbertenes: (a) Abad, A.; Agullo, C.; Cunat, A. C.; Perni, R. H. *J. Org. Chem.* **1999**, *64*, 1741–1744; (b) Ho, T. L.; Chang, M. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2479–2482; (c) Tori, M.; Miyako, T.; Sono, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2731–2738.
4. (a) Mukherjee, D.; Dutta Gupta, P.; Pal, A.; Roy, A. *Tetrahedron Lett.* **2000**, *41*, 7563–7566; (b) Mukherjee, D.; Das, S.; Saha, A. K. *Tetrahedron Lett.* **1994**, *35*, 3353–3354; (c) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 329–332; (d) Banerjee, A. K.; Pena-Matheud, C. A.; de Carrasco, M. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2485–2490; (e) Chandrasekaran, S.; Turner, J. V. *Tetrahedron Lett.* **1982**, *23*, 3799–3802; (f) Leriverend, M. L.; Vazeux, M. *J. Chem. Soc., Chem. Commun.* **1982**, 866–867; (g) Frater, G. *J. Chem. Soc., Chem. Commun.* **1982**, 521–522.
5. Patra, D.; Ghosh, S. *J. Org. Chem.* **1995**, *60*, 2526–2531.
6. Samajdar, S.; Ghatak, A.; Ghosh, S. *Tetrahedron Lett.* **1999**, *40*, 4401–4402.
7. All new compounds reported here were duly characterized on the basis of spectroscopic (IR, ^1H and ^{13}C NMR) and microanalytical (C, H) data. Spectroscopic data for selected compounds: Compound **5**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (3 H, s, Me), 0.89 (3 H, s, Me), 0.97 (3 H, s, Me), 1.49–1.95 (6 H, m), 1.84 (3 H, s, Me), 4.88 (2 H, br s), 5.73 (1 H, d, $J = 15.9$ Hz), 6.06 (1 H, d, $J = 15.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (Me), 20.2 (CH_2), 22.1 (Me), 24.2 (Me), 25.8 (Me), 37.3 (CH_2), 39.7 (CH_2), 44.7 (C), 48.9 (C), 114.5 (CH_2), 129.8 (CH), 138.2 (CH), 142.9 (C). Compound **15**: IR 1841.9, 1778.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.81 (3 H, s, Me), 0.98 (3 H, s, Me), 1.07 (3 H, s, Me), 1.44 (1 H, t, $J = 8.4$ Hz), 1.63–2.03 (5 H, m), 1.78 (3 H, br s, Me), 2.17 (1 H, br d, $J = 10.5$ Hz), 2.29 (1 H, br s), 2.63 (1 H, d, $J = 13.8$ Hz), 3.42 (2 H, m) and 5.74 (1 H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5 (Me), 19.5

(CH_2), 23.8 (Me), 25.2 (Me), 26.0 (Me), 29.7 (CH_2), 37.1 (CH_2), 40.4 (CH_2), 42.8 (CH), 43.0 (CH), 44.6 (CH), 45.5 (C), 46.2 (C), 125.0 (CH), 137.2 (C), 173.4 (CO), 174.4 (CO). Compound **1**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.56 (3 H, s, Me), 1.07 (3 H, s, Me), 1.26 (3 H, s, Me), 1.55–1.81 (5 H, m), 2.34 (3 H, s, Me), 2.50 (1 H, m), 6.99 (1 H, m), 7.16 (3 H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 (CH_2), 22.2 (Me), 24.7 (Me), 24.8 (Me), 26.9 (Me), 37.2 (CH_2), 40.2 (CH_2), 44.6 (C), 50.9 (C), 124.5 (CH), 126.4 (CH), 127.7 (CH), 128.2 (CH), 137.1 (C), 147.9 (C).

8. Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett*. **1989**, *30*, 6733–6736.
9. The natural enantiomer, (−)-herbertene, exhibits $[\alpha]_D^{14} = -56$ (*c* 1.4, $CHCl_3$).[3a]