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A Synthetic Approach to Cuparane and Herbertane Sesquiterpenoids From A Common Intermediate

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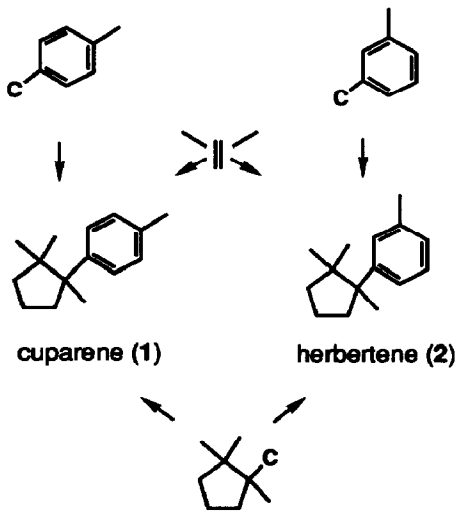
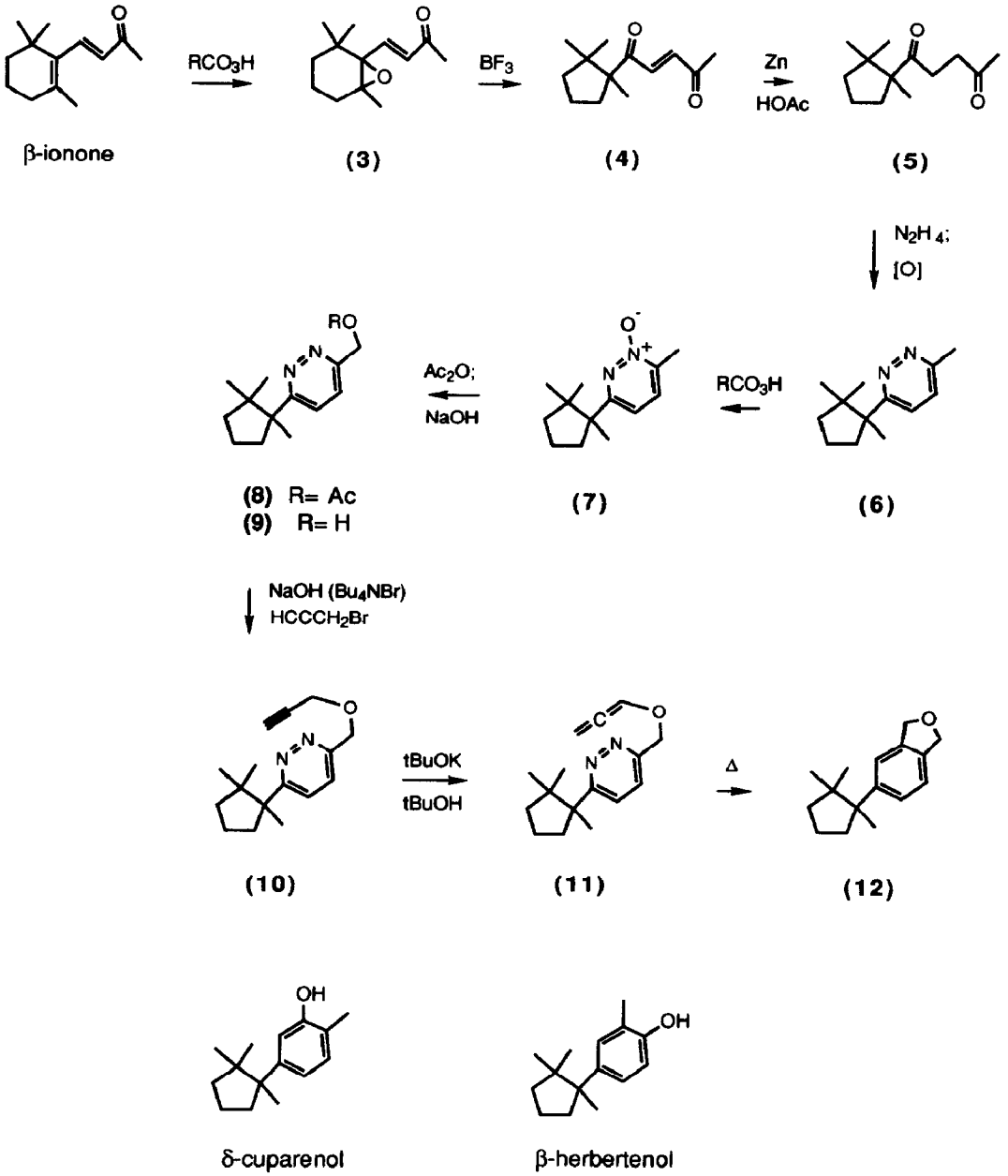
Abstract: A novel route to a common intermediate for the synthesis of both cuparane and herbertane sesquiterpenoids involves *de novo* construction of the aromatic ring by an intramolecular Diels-Alder reaction.

Cuparene (**1**) and herbertene (**2**) are sesquiterpenes which differ in the substitution pattern of the aromatic ring. However, this slight difference makes it impossible to obtain both series of compounds in a synthetic route which starts from an aromatic substance. In fact the many syntheses reported to date invariably adopted this expedient but obvious direction, while addressing methods for elaboration of the cyclopentane moiety which contains two contiguous quaternary carbon centers. We were intrigued by the possibility of gaining access to both skeletons in one stroke which necessarily requires construction of the aromatic ring at a later stage of the synthesis. We describe here our effort in this context.




RCO3H
BF3
Zn
HOAc
β-ionone
(3)
(4)
(5)
N2H4;
[O]
RO
Ac2O;
NaOH
RCO3H
(8) R= Ac
(9) R= H
(7)
(6)
NaOH (Bu4NBr)
HCCCH2Br
tBuOK
tBuOH
Δ
(10)
(11)
(12)
OH
OH
δ-cuparenol
β-herbertenol

Our investigation started from epoxidation of β-ionone. The monoepoxide (**3**) was isomerized to the enedione (**4**) in 72% yield on brief treatment with boron trifluoride etherate[1]. Reduction of the enedione with zinc in acetic acid afforded the γ-diketone (**5**) in 98% yield. This diketone was converted into the pyridazine (**6**) (84% yield) by prolonged reaction with hydrazine hydrate in refluxing ethanol, due to gradual aromatization of the initially formed dihydropyridazines. The pyridazine (**6**) was oxidized with one equivalent of *m*-chloroperbenzoic acid to give the *N*-oxide (**7**) in 96.5% crude yield which was directly used in the next step. The other isomer was not formed in any detectable amount according to tlc and nmr evidence, apparently due to steric inhibition. The Polonovski reaction product of this *N*-oxide in refluxing acetic anhydride was the acetate (**8**) (46% yield) and it was promptly saponified to give the primary alcohol (**9**) (92% yield).

At this stage we studied the Diels-Alder reaction of alcohol (**9**) as well as pyridazine (**6**). Unfortunately the reactions of (**6**) failed uniformly with dienophiles such as methyl vinyl ketone and acrylic acid under reaction conditions involving temperatures up to 260°C. A preliminary high pressure experiment was not encouraging either. Intramolecular Diels-Alder reactions were then attempted, but after derivatizing the alcohol (**9**) into the acrylic ester and the vinyldimethylsilyl ether, in both cases the desired transformation still remained unobserved in numerous trials. At this juncture the use of an allenyl ether was considered as substrate on the basis of reports[2] which indicate a high dienophilic reactivity of such compounds toward unactivated dienes in intramolecular Diels-Alder reactions. The alcohol (**9**) was alkylated with propargyl bromide in a two-phase system of water and dichloromethane in the presence of tetra-*n*-butylammonium bromide and the resulting propargyl ether (**10**) (75% yield) was isomerized to furnish the allenyl ether (**11**) in almost quantitative yield by potassium *t*-butoxide in refluxing *t*-butanol. When a toluene solution of this allenyl ether was placed in a teflon vessel and heated in a resealable bomb at 200°C for 20 h the cyclic ether (**12**) was produced, albeit in 22.4% yield. Apparently the Diels-Alder reaction was not the best pathway available to the allenyl ether, but once the cycloaddition was concluded, the logical events of dinitrogen elimination from the adduct and double bond migration into the six-membered ring followed.

The usefulness of ether (**12**) in the elaboration of sesquiterpenoids possessing the cuparane and herbertane skeletons is evident. Particularly the access to oxygenated members of these two series of compounds (e.g. δ–cuparenol and β-herbertenol) is predictable, for example via oxidation to two isomeric phthalides. Work is in progress.[3]

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References and Notes

1. Frei, B.; Eichenberger, H.; von Wartburg, B.; Wolf, H.R.; Jeger, O. *Helv. Chim. Acta* **1977,** *60,* 2968.
2. Nagashima, S.; Kanematsu, K. *J. Synth. Org. Chem. (Jpn)* **1993,** *51,* 608.

3. All new compounds except the *N*-oxide (**7**), which was used directly without further purification, have correct elemental analyses and/or parent peaks in the high resolution mass spectra.
Some supporting spectral data of other compounds are as follows: (**4**) IR 1677 cm^{-1}; 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.86 (3H, s), 1.10 (3H, s), 1.20 (3H, s), 1.42-1.80 (5H, m), 2.36 (3H, s), 2.4-2.5 (1H, m), 6.90 (1H, d, J=15.3 Hz), 7.24 (1H, d, J=15.3 Hz). (**5**) IR 1720, 1697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.82 (3H, s), 1.06 (3H, s), 1.13 (3H, s), 1.4-1.8 (5H, m), 2.19 (3H, s), 2.40 (1H, m), 2.60-2.82 (4H, m). (**6**) ^{1}H-NMR ($CDCl_3$) δ 0.49 (3H, s), 1.06 (3H, s), 1.27 (3H, s), 1.4-1.82 (5H, m), 2.58 (3H, s), 2.6-2.8 (1H, m), 7.14 (1H, d, J=9 Hz), 7.27 (1H, d, J=9 Hz). (**7**) ^{1}H-NMR ($CDCl_3$) δ 0.63 (3H, s), 1.11 (3H, s), 1.29 (3H, s), 1.45-1.85 (5H, m), 2.2-2.3 (1H, m), 2.48 (3H, s), 7.01 (1H, d, J=8.4 Hz), 7.45 (1H, d, J=8.4 Hz). (**8**) IR 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.54 (3H, s), 1.13 (3H, s), 1.34 (3H, s), 1.4-1.9 (5H, m), 2.13 (3H, s), 2.80 (1H, m), 5.38 (2H, s), 7.42 (2H, q, J=5.1 Hz). (**9**) IR 3300 cm^{-1} (br); ^{1}H-NMR ($CDCl_3$) δ 0.48 (3H, s), 1.07 (3H, s), 1.28 (3H, s), 1.40-1.85 (5H, m), 2.60-2.8 (1H,m), 4.91 (2H, s), 7.42 (1H, d, J=9 Hz), 7.48 (1H, d, J=9 Hz). (**10**) IR 3300 cm^{-1} (sh); ^{1}H-NMR ($CDCl_3$) δ 0.54 (3H, s), 1.13 (3H, s), 1.35 (3H, s), 1.5-1.9 (5H, m), 2.50 (1H, d, J=2.1 Hz), 2.7-2.9 (1H, m), 4.28 (2H, d, J=2.4 Hz), 4.89 (2H, s), 7.46 (1H, d, J=9 Hz), 7.50 (1H, d, J=9 Hz). (**11**) ^{1}H-NMR ($CDCl_3$) δ 0.55 (3H, s), 1.15(3H, s), 1.36 (3H, s), 1.5-1.9 (5H, m), 2.8 (1H, m), 4.95 (2H, s), 5.43 (2H, d, J=5.7 Hz), 6.82 (1H, t, J=5.7 Hz), 7.40 (1H, d, J=8 Hz), 7.42 (1H, d, J=8 Hz). (**12**) H-NMR ($CDCl_3$) δ 0.56 (3H, s), 1.07 (3H, s), 1.27 (3H, s), 1.4-1.8 (5H, m), 2.5 (1H, m), 5.09 (4H, s), 7.13 (1H, d, J=8 Hz), 7.21 (1H, s), 7.27 (1H, d, J=8 Hz).

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