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Stereoselective Synthesis of *trans*-Hydroazulene Derivatives by Tandem Michael–Intramolecular Wittig Reactions of a Cyclic Phosphonium Ylide with Alkyl or Aryl 1-Cyclopentenyl Ketones

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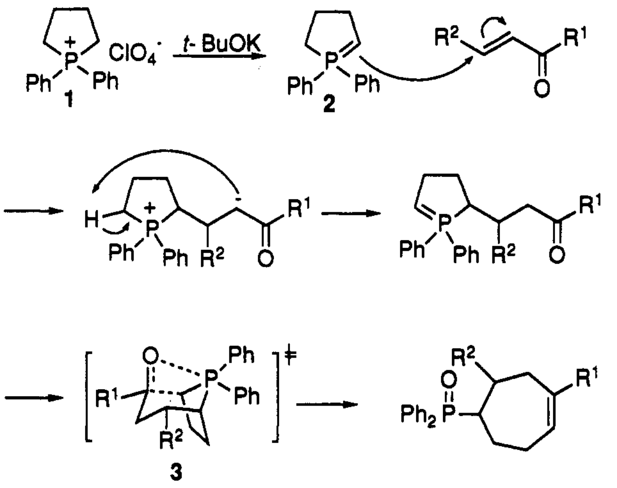
Summary: The reaction of 1-cyclopentenyl ketones **4a–c** with 1,1-diphenylphospholanium ylide **2** gave *trans*-hydroazulene derivatives **5a–c** with high diastereoselectivity *via* tandem Michael–intramolecular Wittig reactions.

The reaction of a cyclic phosphonium ylide[1] with an aldehyde followed by Horner–Wittig reaction of the resulting phosphine oxide with a second aldehyde provides a method for the construction of trienes,[2] unconjugated dienes,[3] and unconjugated enones.[4] We recently reported[5] that reaction of the ylide generated from five-membered cyclic phosphonium salt **1**[1] with α,β-unsaturated ketones yields cycloheptenyldiphenylphosphine oxides in a one-pot reaction through Michael addition of the ylide[6] followed by regeneration of an ylide *via* proton transfer and then intramolecular Wittig reaction[7] (Scheme I). A phosphabicyclic transition state **3** was proposed for the intramolecular Wittig reaction, suggesting that the relative stereocontrol of the groups substituted on the cycloheptene ring would be accomplished. In this work, we attempted to use this reaction for the stereoselective synthesis of a hydroazulene skeleton[8] which provides the basic ring system of natural products such as the guaianolide sesquiterpenes.[9]

Scheme I



The reaction of 1-cyclopentenyl phenyl ketone **4a**[10] with the ylide generated from **1** in the presence of *t*-BuOK was carried out under the same reaction conditions as in the previous paper.[5] After purification by column chromatography, the hydroazulene derivative **5a** formed by the tandem Michael–intramolecular Wittig reactions was isolated in 66% yield along with a small amount of diene **6a** (4% yield) (Table I).

The structure of **5a** was confirmed by ^{13}C NMR, ^{13}C DEPT, and ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis. In the ^{13}C NMR spectrum,[11] three pairs of doublets with characteristic coupling constants (J_{PC})[12] corresponding to carbons α, β, and γ to phosphorus were observed in the range 40–50 ppm. These peaks were assigned to the two bridgehead carbons and the carbon α to phosphorus in the hydroazulene skeleton. No peaks from the other possible stereoisomers were observed in that range, indicating that the relative stereochemistry of the adjacent three methine carbons (C_4, C_{3a}, and C_{8a}) was highly controlled. X-ray crystallography of **5a**[13] showed a trans-fused hydroazulene in which H_{3a} and H_4 also had a trans relationship. The relative configuration and the

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[11] **5a**: ^{13}C NMR (peaks of higher field than 50 ppm) δ 23.6 (C_2), 26.0 (C_3, $^3J_{PC} = 6.4$ Hz), 27.3 (C_5, $^2J_{PC} = 2.0$ Hz), 32.4, 34.5 (C_1 or C_6), 42.9 (C_{3a}, $^2J_{PC} = 2.9$ Hz), 44.2 (C_4, $^1J_{PC} = 68.4$ Hz), 48.2 (C_{8a}, $^3J_{PC} = 14.2$ Hz).

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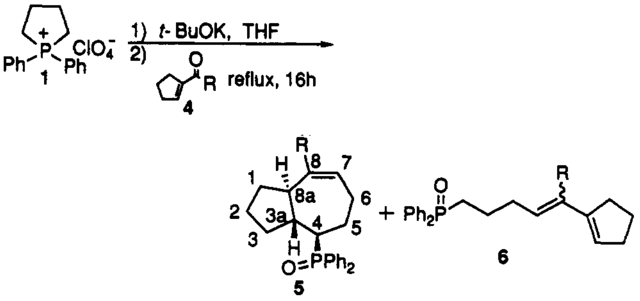
Table I. Reaction of the Ylide from 1 with 4a–c

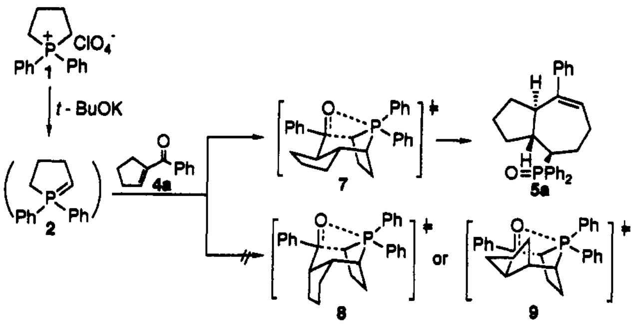


entry	R	ketone	yield[a] (%) hydroazulene 5	diene 6
1	Ph	4a	66 (5a)	4 (6a)
2	$CH_3(CH_2)_2$	4b	64 (5b)[b]	8 (6b)
3	$(CH_3)_2CH$	4c	53 (5c)[b]	1 (6c)

[a] Isolated yield. [b] An additional unseparated mixture of hydroazulene 5 and diene 6 (less than 1% for entry 2 and 1% for entry 3) was also obtained.

high stereoselectivity can be accounted for by considering likely transition states (Scheme II). Among them, the transition state 7 in which the cyclopentane ring is fused to the six-membered ring in phosphabicycle in an equatorial–equatorial manner is thought to be more favorable than the other possible transition states (8 or 9) because of 1,3-diaxial interactions. Consequently, the trans–trans hydroazulene derivative substituted by a $Ph_2P(O)$ group would be obtained from the rigid transition state 7 with high stereoselectivity.

Scheme II



Hydroazulene derivatives **5b–c**[14] were similarly obtained from reaction of the cyclic phosphonium ylide **2** with cyclopentenyl ketones **4b–c**[10] in 64 and 53% yield, respectively, accompanied by small amounts of the normal Wittig product **6b–c**. Each of the hydroazulenes was obtained as a single stereoisomer where the relative stereochemistry was deduced to be the same as **5a** based on the similarity of the chemical shifts and coupling constants (J_{PC}) for the three sp^3 methine carbons.

Acknowledgment. We are grateful to Ihara Chemical Co., Ltd. for a gift of triphenylphosphine.

Supplementary Material Available: Experimental procedure for the reaction of **2** with **4a–c** and ^{1}H and ^{13}C NMR spectra of **5a–c** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) Crystallographic data for **5a**: Mo Kα radiation, $C_{28}H_{29}OP$, a = 29.61(3) Å, b = 5.784(4) Å, c = 26.620(8) Å, β = 98.52(6)^0, V = 4509(5) Å^3, monoclinic with space group $C2/c$, Z = 8, ρ(calcd) = 1.215 g cm^{-3}. The structure was solved by direct methods, R = 0.046 and Rw = 0.042. The authors have deposited atomic coordinates for **5a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(14) **5b**: ^{13}C NMR (peaks of higher field than 50 ppm) δ 14.0 ($C_{3'}$), 22.0 ($C_{2'}$), 24.1 (C_2), 26.0 (C_3, $^3J_{PC}$ = 9.3 Hz), 27.4 (J_{PC} = 1.5 Hz), 29.7 (J_{PC} = 1.0 Hz) (C_1 or C_5), 33.9 (C_6, $^3J_{PC}$ = 1.0 Hz), 38.5 ($C_{1'}$), 42.5 (C_{3a}, $^2J_{PC}$ = 2.9 Hz), 45.4 (C_4, $^1J_{PC}$ = 67.9 Hz), 48.3 (C_{8a}, $^3J_{PC}$ = 14.7 Hz). **5c**: ^{13}C NMR (peaks of higher field than 50 ppm) δ 22.6, 23.2 (CH_3 in *i*-pr), 24.2 (C_2), 25.9 (C_3, $^3J_{PC}$ = 9.8 Hz), 27.3, 29.5 (C_1 or C_5), 31.2 ($C_{1'}$), 33.8 (C_6), 42.7 (C_{3a}, $^2J_{PC}$ = 2.4 Hz), 45.4 (C_4, $^1J_{PC}$ = 68.4 Hz), 48.9 (C_{8a}, $^3J_{PC}$ = 14.2 Hz).