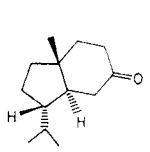
Communications

Intramolecular Routes to Hydrindanes: The Diels-Alder and Michael-Aldol Approach to 6-Isopropyl-9-methylbicyclo[4.3.0]nonan-3-one†

Summary: Two stereoselective syntheses of 6-isopropyl-9-methylbicyclo[4.3.0]nonan-3-one (**1**) are described. These include an intramolecular Michael–Aldol reaction sequence from ketoaldehyde **7** and an internal Diels–Alder cycloaddition route from triene **9**. Zirconium *n*-propoxide provides the best selectivity in the base-catalyzed reactions and thus affords a direct preparation of the left-hand portion of retigeranic acid.

Sir: The bicyclo[4.3.0]nonane (hydrindane) nucleus is widely encountered in nature in a variety of natural products, particularly steroids and terpenes. Consequently many different construction procedures have been developed, including annulation,[1-7] conjugate addition/alkylation (acylation),[8-11] internal Michael–Aldol,[12,13] and intramolecular Diels–Alder reactions[14-21] for the synthesis of the hydrindane skeleton in a stereocontrolled manner. We report the preparation of the *trans*-hydrindanone **1** (6-isopropyl-9-methylbicyclo[4.3.0]nonan-3-one) required for our approach to retigeranic acid (**2**).[22] The total



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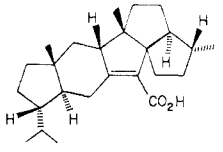

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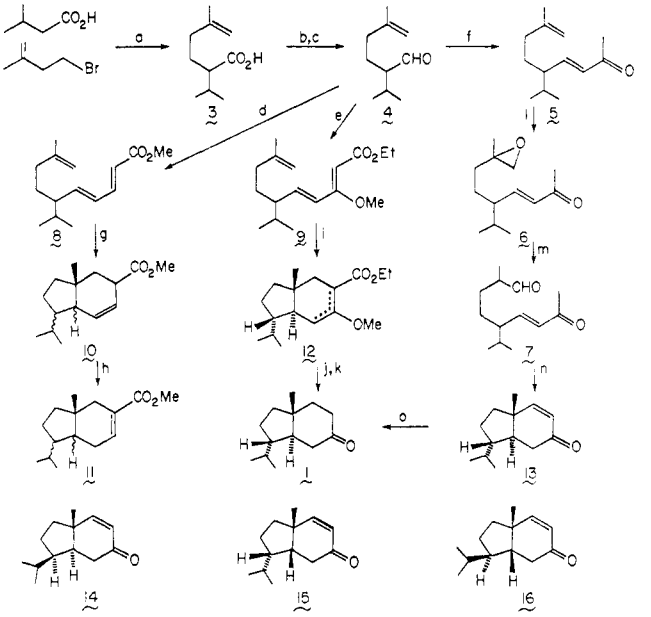
synthesis of this interesting pentacyclic sesterterpene is currently the object of intense study by several investigators.[23-28] Recently the ketone **1** has also been synthesized by Corey and Engler[26] and subsequently Evans and Morrissey[29] reported a modification of their sequence.

Scheme I[a]



[a] (a) NaH, THF, 65 °C, 10 min; LiN(*i*-Pr)$_2$, 0 °C to 30 °C, 24 h; (b) LiAlH$_4$, ether, 0 °C to 22 °C, 1 h; (c) PCC, NaOAc, CH_2Cl_2, 22 °C, 3 h; (d) $(MeO)_2POCH_2CH{=}CHCO_2Me$, LiN(*i*-Pr)$_2$, THF, HMPA, 22 °C, 1 h; (e) $(MeO)_2POCH_2(MeO)C{=}CHCO_2Et$, LiN(*i*-Pr)$_2$, THF, HMPA, −78 °C to 22 °C, 1 h; (f) $(MeO)_2POCH_2COMe$, KOH, MeOH, H_2O, 22 °C, 5 h; (g) *p*-$Cl_2C_6H_4$, 173 °C, 24 h; (h) NaOH, MeOH, 22 °C, 72 h; (i) *p*-$Cl_2C_6H_4$, 173 °C, 72 h; (j) concentrated HCl, THF, 22 °C, 0.5 h; (k) LiCl, H_2O, Me_2SO, 155 °C, 2.5 h; (l) *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C, 4 h; (m) $BF_3{\cdot}Et_2O$, C_6H_6, 22 °C, 0.5 min; (n) Zn(O-*n*-Pr)$_4$, C_6H_6, LiOH, 22 °C, 12 h; $(CF_3CO)_2O$, DBU, 4-DMAP, CH_2Cl_2, −78 °C to 22 °C, 2 h; (o) H_2, 10% Pd/C, EtOAc, 30 psi, 22 °C, 1 h.

Synthesis of the desired ketone **1** by both an intramolecular Diels–Alder and internal Michael–Aldol sequence appeared particularly interesting, as it would permit the direct comparison of the level of stereocontrol available in these reactions with more highly substituted precursors than have been studied previously. Suitable trienes **8** and **9** and the ketoaldehyde **7** were prepared, as outlined in Scheme I, via Horner–Wadsworth–Emmons condensation with the aldehyde **4**. This aldehyde was synthesized in 68% overall yield as illustrated, commencing with the

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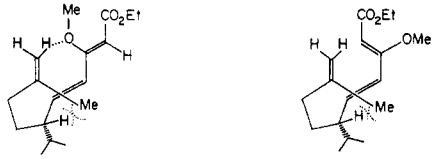
alkylation of the mixed sodium/lithium dianion of 3-methylbutyric acid with 4-bromo-2-methylbutene. (Complete experimental details are available as supplementary material.)

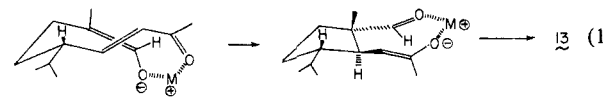
Cyclization of triene-ester **8** was effected in refluxing *p*-dichlorobenzene for 24 h to give after chromatography a 96% yield of adducts **10**. To facilitate analysis of the mixture, the double bond was isomerized into conjugation with sodium hydroxide in dry methanol to give **11**. The 400-MHz ^{1}H NMR spectrum revealed the presence of eight isopropyl methyl signals (δ 0.80, 0.81, 0.83, 0.84, 0.87, 0.89, 0.89, 0.91) and indicated that all four stereoisomers were present. The ratio of the trans/cis ring systems (5:3) was established by integration of the cis (0.94) and trans (0.72, shielded by double bond) methyl singlets. In contrast, cycloaddition of **9** (72–90 h, 80%) proceeded with significantly higher selectivity. Isomer analysis was complicated by the presence of conjugated ester adducts **12**, thus the mixture was subjected to hydrolysis (HCl/H_2O) and decarboxylation ($LiCl/Me_2SO$). The single ketone isomer **1** was obtained (~34% yield from **4**),[26,30] indicating that the major adduct possessed the required stereochemistry.

Examination of molecular models does not suggest an obvious reason for the selectivity imparted by the methoxy substituent. Nevertheless a tentative explanation may be advanced. It seems likely that a preferred conformation of **9** is the s-trans arrangement, which allows a favorable association of the vinyl hydrogen with the oxygen lone pair.



Rotation about the single bond places the diene unit in the correct orientation for cyclization to give the observed product, in which the isopropyl function has the required stereochemistry. This avoids an unfavorable nonbonded interaction between the isopropyl substituent and the vinyl methyl group in the transition state and is consistent with the recently proposed "twist-asychronous" model for related systems in which the internal (cyclopentane) bond forms preferentially.[31] Unfortunately, in spite of the desired stereochemical result, this cyclization proved rather capricious, and although reproducible on several occasions a fresh bottle of *p*-dichlorobenzene afforded significantly reduced yields (isolated adduct 15–20%).[32] The use of 1,2,4-trichlorobenzene (bp 214 °C, 38 h) provided some improvement (54% yield), but on a preparative scale the following sequence is preferable.

Selective epoxidation of the remote double bond in **5** was realized with *m*-chloroperbenzoic acid and the resulting epoxide **6** (92%) isomerized with boron trifluoride etherate to give the ketoaldehyde **7** (75%). In parallel with the earlier results of Stork and collaborators,[12,13] the best stereoselectivity in the conjugate addition step was achieved with zirconium *n*-propoxide [$Zr(O\text{-}i\text{-}Pr)_4$ was unsatisfactory]. In addition to a bulky counterion, the zirconium formed a tighter bond to oxygen than the others examined, (see Table I) leading to the most trans-fused product. These reactions probably proceed via a highly ordered cyclic transition state, as illustrated in eq 1. The



(1)

nonbonded interactions are thus minimized so the isopropyl group may adopt the desired trans geometry with respect to the quaternary methyl substituent and the two oxygen bearing side chains occupy a preferred trans orientation. If desired, the ketols may be isolated, but they were readily dehydrated directly to the unsaturated ketones **13–15** with trifluoroacetic anhydride/1,8-diazabicyclo[5.4.0]undec-7-ene in dichloromethane containing 4-(dimethylamino)pyridine. The distinctive ^{1}H NMR features of these unsaturated ketones, in which the β-vinyl hydrogen falls below δ 7.0 in the trans-hydrindenone series vs. δ 6.5 for the cis-fused systems, facilitated the stereochemical assignments[12] (**13**, 7.13; **14**, 7.08; **15**, 6.53). Additional support is provided by the tertiary methyl signals at δ 0.95, 1.02, and 1.22, respectively. The all-cis isomer **16** could not be detected and does not appear to be formed. Hydrogenation of **13** afforded the desired saturated ketone **1** in 94% yield (~40% from **4**).

Table I. Base-Catalyzed Cyclization of Ketoaldehyde 7

entry	base	yield, %	product ratio 13	14	15
1	NaOMe	80	3.4	1.2	1
2	$Mg(OMe)_2$	51	10	1.5	1
3	$Zr(O\text{-}n\text{-}Pr)_4$	80	10	1	1

In summary, both intramolecular routes afforded the hydrindanone **1** and provide a direct preparation of the left-hand portion of retigeranic acid (**2**). However, the internal Michael–Aldol condensation sequence was superior. These concepts may be extended to the construction of other more complex ring systems and this is currently being pursued.

Acknowledgment. We are grateful to Memorial University of Newfoundland and the Natural Sciences and Engineering Research Council of Canada for financial support of this research, B. Gregory for high resolution mass spectra, H. J. Liu (University of Alberta) for 400-MHz ^{1}H NMR spectra, and the referees for their comments.

Note Added in Proof A total synthesis of (±)-retigeranic acid has just been published in which ketone **1** was utilized as a key intermediate: Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339.

Supplementary Material Available: Experimental details and spectral assignments for the new compounds prepared in this work (8 pages). Ordering information is given on any current masthead page.

(30) We thank Professor Corey for copies of the ^{1}H NMR spectra of **1** and its cis isomer.

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(32) In spite of refluxing fresh samples of *p*-dichlorobenzene for several days and exposing them to light and/or air the yields were less (reduced up to 65%) than in the earlier experiments. It appears that a minor contaminant in some commercial samples of *p*-dichlorobenzene acts as a catalyst. Attempted catalysis with Lewis acids was unsuccessful and added pyridine or the use of tri-*n*-butylamine as solvent did not restore the higher yields. At present 1,2,4-trichlorobenzene is the best alternative.

† Dedicated to Professor Raymond U. Lemieux on the occasion of his 65th birthday.

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