Synthetic and Structural Studies of Key Intermediates toward Forskolin and/or Erigerol. Relative Stereochemistry, Conformational Preferences and Stereoselectivity Control

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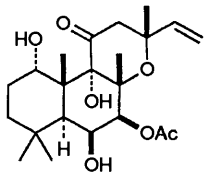
An alternative stereoselective synthesis of compound **9c**, an intermediate in the synthesis of the highly oxygenated diterpene erigerol **2**, was accomplished through an organometallic addition to the α,β-unsaturated ketone **7**, followed by osmylation and protection of the resultant diol. In spite of the fact that the addition of the lithio derivative of *N,S*-dimethyl-*S*-phenylsulfoximide occurred exclusively from the β face of enone **7**, this approach to the alcohol **8c**, a key intermediate toward forskolin **1**, is not suitable because of the low yield of the osmylation step. With the aid of one- and two-dimensional NMR techniques and a series of NOE experiments, the complete stereochemistry and conformational preferences of alcohols **8a**, **8c**, **9a** and **9c** were established. The lowest-energy conformations of alcohols **8a**, **8c** and **9c**, based on molecular mechanics calculations, confirmed the results obtained by NMR spectroscopy.

Forskolin **1**[1] is a highly oxygenated diterpene that has generated an enormous amount of synthetic interest[2] due to its unique structural features and its broad range of biological activities.[3] The related diterpene erigerol **2**[4] with a structural complexity comparable to that of forskolin **1**, has also received attention from a synthetic viewpoint.[5] Recently, we have developed alternative sequences for the preparation of the Ziegler key intermediate **3** and its diastereoisomer **4**, for the synthesis of forskolin and erigerol, respectively.[6] Now, we report the results of additional efforts tending to improve the availability of both intermediates and to gain an understanding of the reactivity of related compounds.



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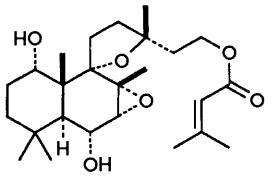

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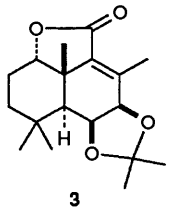

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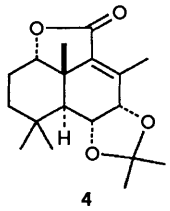

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The present work deals with two different aspects of the synthetic sequences developed in our previous work, one of which is outlined in the Scheme 1.[6a] The first aspect relates to the alkylation of the C-8 carbonyl group at a different stage in the synthetic sequence by using the enone acetal **7** as starting material. Toward this end, we considered the use of organocerium and organoytterbium reagents in merit of their ability to effect 1,2-carbonyl additions in highly hindered and enolizable α,β-unsaturated substrates.[7] The second aspect deals with the influence that such alkylation has upon the stereoselectivity of the C-6 and C-7 hydroxylation reaction which, when using the acyloxy group as an auxiliary diastereofacial control agent, occurs with a 3:1 preference from the β-face of the molecule (**6b**, Scheme 1).[6a] Furthermore, to select properly the most adequate auxiliary group it would be convenient to know the stereochemistry of the addition products as well as their ring B conformational preferences. Unfortunately, neither the ^{1}H and ^{13}C NMR chemical-shift values of the tertiary alcohols derived from enone **7** nor those from the saturated ketone **10** allowed the use of any reliable correlation to assign their C-8 methyl group configuration directly.[8] Therefore, it was necessary to undertake an exhaustive spectroscopic study, on a series of related compounds (Scheme 1), to determine their relative stereochemistry. Finally, based on these results and literature precedents[9] we chose the sulfoximide approach for the transformation of enone **7** into lactone **3**, in the hope of providing the necessary assistance to obtaining the desired stereochemistry in the osmylation step, for the simultaneous introduction of the C-8 methyl group[10] and, eventually, for the preparation of compound **3** in optically active form.[11,12]

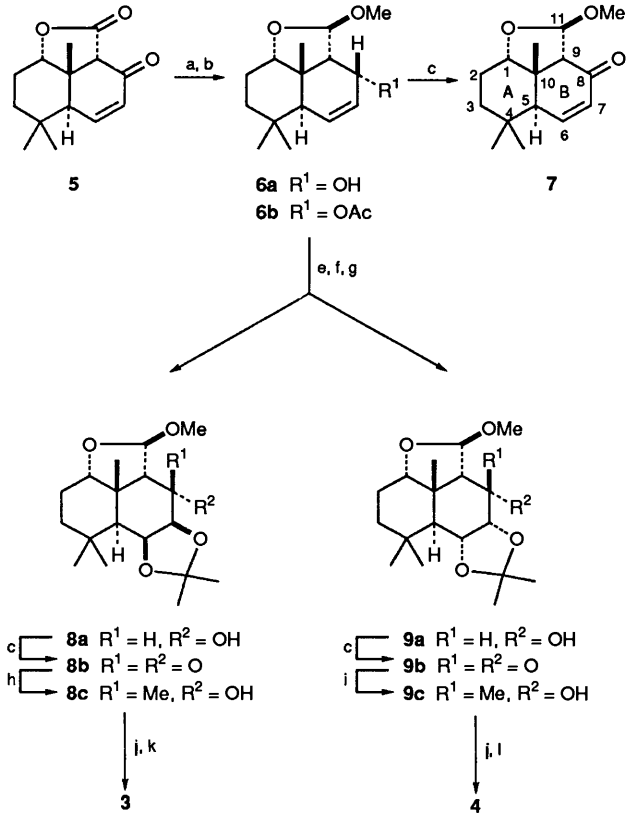
Results and Discussion

As shown in Table 1, a series of experiments was first carried out in order to select the best reaction conditions for the alkylation of enone **7**. In agreement with our previous observations,[13] the use of organomagnesium and organolithium reagents, under standard reaction conditions, afforded a mixture of tertiary alcohols in poor yields (< 35%). Both organocerium[14] and organoytterbium[15] reagents provided a notable increase in yield, however with modest stereoselectivity even at temperatures as low as −90 °C. With the tricyclic saturated ketone **10** better stereoselectivity and excellent yields were obtained when working at 0 °C. Although the actual configuration of these tertiary alcohols could not be determined at this juncture, the ratio of both epimers was easily estimated by ^{1}H NMR spectroscopy, by comparison of the areas under the signals at δ 4.91

Table 1 Conversion of ketones **7** and **10** into the mixture of tertiary alcohols **11a**, **11b** and **12a**, **12b**, respectively

Entry	Reagent/Substrate	T/°C	MeX:$LnCl_3$:Substrate	C-8 Epimer (ratio)	Yield (%)
1	*a*/**7**	25	1.30:0:1.00	**11a**:**11b** (5.5:1)	35
2	*b*/**7**	0	1.30:0:1.00	**11a**:**11b** (2.0:1)	30
3	*c*/**7**	25	1.64:1:0.36	**11a**:**11b** (2.2:1)	97
4	*d*/**7**	25	3.80:1:0.27	**11a**:**11b** (2.2:1)	98
5	*d*/**7**	0	4.80:1:0.27	**11a**:**11b** (2.2:1)	98
6	*d*/**7**	−90	3.80:1:0.27	**11a**:**11b** (2.8:1)	85*
7	*e*/**7**	0	4.90:1:0.27	**11a**:**11b** (2.4:1)	80*
8	*e*†/**7**	−90	3.80:1:0.27	**11a**:**11b** (3.5:1)	83*
9	*a*/**10**	0	1.30:0:1.00	**12a**:**12b** (5.0:1)	40
10	*b*/**10**	0	1.30:0:1.00	**12a**:**12b** (2.5:1)	30
11	*c*/**10**	0	3.80:1:0.28	**12a**:**12b** (6.0:1)	97
12	*d*/**10**	0	3.80:1:0.28	**12a**:**12b** (5.6:1)	98

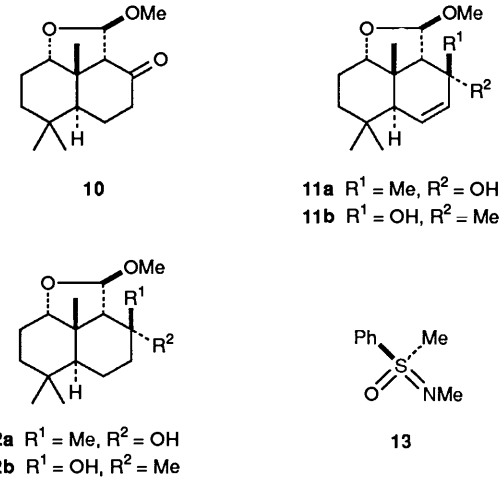
[a] MeMgI. [b] MeLi. [c] MeLi–$CeCl_3$. [d] MeLi–$YbCl_3$. [e] MeMgBr–$YbCl_3$. * Incomplete reaction (5–7% recovered unchanged substrate). † Inverse addition.



Scheme 1 *Reagents:* (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_2Cl_2, EtOH; (b) MeOH, PTSA (cat); (c) PDC, CH_2Cl_2; (d) Ac_2O, pyridine, DMAP (cat); (e) OsO_4, pyridine; (f) $Me_2C(OMe)_2$, PTSA (cat); (g) K_2CO_3, MeOH; (h) MeMgI, Et_2O; (i) MeLi, Et_2O; (j) Jones reagent, acetone; (k) $SOCl_2$, pyridine; (l) KOH, dioxane

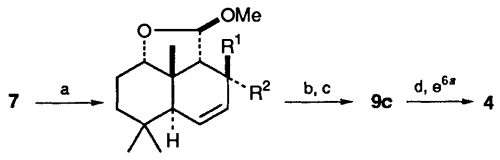
and 5.34 assigned to 11-H for the alcohols **11a** and **11b** derived from enone **7** and the corresponding ones at δ 4.69 and 5.09 for those derived from ketone **10** (alcohols **12a** and **12b**).

Without separation, the mixture of tertiary alcohols obtained by methylation of enone **7** (entry 5, Table 1) was then hydroxylated (osmium tetraoxide under stoicheiometric conditions), and protected [2,2-dimethoxypropane, toluene-*p*-sulfonic acid (PTSA)] affording a sole product in 56% overall yield. This product was identical with compound **9c** (Scheme 1).[6a] The present route to compound **9c** (Scheme 2), apart from providing a direct and simple access to lactone **4**, was useful to show, based on the spectral analysis discussed below, that the attack of the nucleophile on the carbonyl group of enone **7** occurs preferentially from the β face of the enone system to give α-alcohol **11a** as the major product. In addition, it was shown that this particular stereochemistry at C-8 greatly increases the stereoselectivity of the hydroxylation step from the α-face of the molecule. That the nucleophilic attack occurs also preferentially from the β-face of the tricyclic saturated ketone **10** was shown by catalytic hydrogenation of the mixture of allylic alcohols **11a** and **11b** which gave a mixture of tertiary alcohols in which compound **12a** was the major product.



In view of the foregoing results, we decided to apply the Johnson sulfoximide protocol[9,11] in order to increase the stereoselectivity of the hydroxylation of the double bond of enone **7** from the β-face of the molecule, thus allowing a more efficient access to lactone **3**. As expected, treatment of enone **7** with the lithio derivative of (±)-*N*,*S*-dimethyl-*S*-phenylsulfoximide **13** proceeded with excellent facial selectivity to afford a chromatographically separable mixture of two β-hydroxy sulfoximides **14**, diastereoisomeric at sulfur, in good yield. The transformation of the β-hydroxy sulfoximides into the tertiary alcohol **12a** by treatment with Raney nickel[10] clearly indicated that the addition had occurred exclusively from the β-face of enone **7**. Finally, when the less polar β-hydroxy sulfoximide was treated with osmium tetraoxide under stoichiometric conditions the corresponding osmate was readily formed (TLC); however, and presumably due to its great stability, this osmate's hydrolysis to the diol was very slow, even under a variety of reaction conditions.* Nevertheless, protection of the resultant mixture (2,2-dimethoxypropane, PTSA) afforded compound **15** but in low yield. In turn, desulfurization of **15** gave alcohol **8c**, identical with the tertiary alcohol (see Scheme 1) obtained in

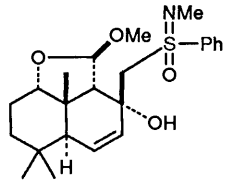
* We thank Professor C. R. Johnson for the experimental details of the reactions described in his communication, ref. 9.



11a R^1 = Me, R^2 = OH
11b R^1 = OH, R^2 = Me

Scheme 2 *Reagents:* (a) MeLi, $YbCl_3$, THF; (b) OsO_4, pyridine; (c) $Me_2C(OMe)_2$, PTSA (cat); (d) Jones reagent, acetone; (e) KOH, dioxane

our previous work *en route* to forskolin **1**.[6a] In spite of the favourable stereoselectivity in the addition of the lithiated sulfoximide to enone **7**, the low yield in the preparation of compound **15** makes this sequence of low synthetic value. Attempted hydroxylation of the β-hydroxy sulfoximides with osmium tetraoxide under catalytic conditions was unsuccessful; they reacted very slowly under a variety of reaction conditions.*



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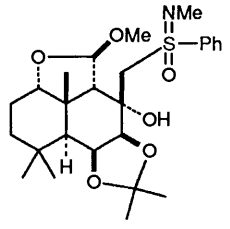

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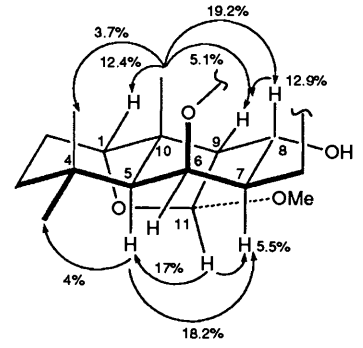
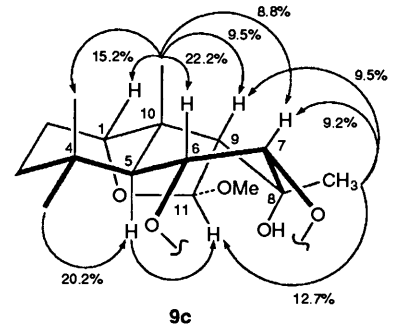
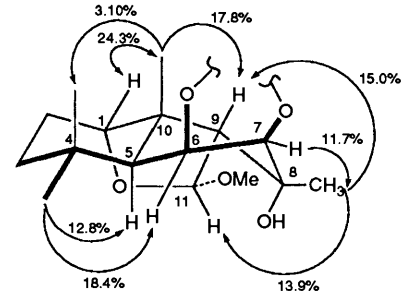
Spectral analysis, necessary for the unambiguous determination of the relative stereochemistry and conformational preferences of the series of compounds described above, was initiated with the alcohol **9a** (Scheme 1). The ^1H NMR signals of 1-, 5-, 6-, 7-, 8-, 9- and 11-H of compound **9a** were easily assigned on the basis of chemical-shift considerations and the complete assignment was made through ^1H–^1H COSY 90 measurements and a series of nuclear Overhauser enhancement (NOE) experiments,[16] which further confirms the relative stereochemistry at C-1, -5, -6, -7, -8, -9 and -11 of this compound. The ^1H NMR spectral data of compound **9c**, obtained by addition of methyllithium to ketone **9b** (Scheme 1)[6a] or by the sequence descibed in this report (Scheme 2), are very similar to those of compound **9a**, except for the lack of the signal at δ 4.19 corresponding to 8-H and the presence of an additional methyl signal at δ 1.25 tentatively attributed to the C-8 methyl protons. The NOE experiments on tertiary alcohol **9c** (Fig. 1) follow the same general pattern as those for secondary alcohol **9a**. In addition, when the signal at δ 1.25 was irradiated, the signals of 7-, 9- and 11-H were enhanced confirming its assignment to the C-8 methyl group, establishing its β orientation and further, suggesting a preferred twist-boat conformation for ring B of this compound. In a similar way, a series of NOE experiments showed that, in compound **8a**, irradiation of the signal at δ 1.37, attributed to the methyl of C-10, enhanced those of 1-, 8-, 9-H and that of the β-methyl group at C-4, while irradiation at δ 4.93 (11-H) enhanced the signals of 5- and 7-H. These results are an indication of the chair-like conformation of ring B and also of the equatorial position of the hydroxy group at C-8 (Fig. 1). The NOE experiments on the tertiary alcohol **8c**, obtained by a Grignard reagent addition to ketone **8b** (Scheme 1)[6a] or by desulfurization of compound **15**, showed the following results. Irradiation at the signal at δ 3.75, assigned to 1-H, enhanced the methyl signal at δ 1.41 assigned, consequently, to the methyl group at C-10 which, in turn, on irradiation showed NOE with 1- and 9-H signals and also with the three-proton signal at δ 1.07, assigned to the β methyl group at C-4 and finally, by irridiation



8a



9c



8c

Fig. 1 Relative stereochemistry of compounds **8a**, **9c** and **8c** and proton–proton through-space connectivities, obtained by NOE difference experiments

of the signal at δ 3.93 corresponding to 7-H, enhancements of the signals at δ 1.30 attributed to one of the methyl groups of the isopropylidene moiety, and at δ 1.34, already assigned to the methyl group at C-8, were observed, thus confirming the attribution of the latter (Fig. 1). The values of the coupling constants $J_{5\text{-H},6\text{-H}}$ of 2.0, and that of $J_{6\text{-H},7\text{-H}}$ of 8.05 Hz, which correspond to torsion angles of 63 and 31°, respectively, (64 and 31° for a typical twist-boat conformation)[17] and the lack of an observable effect in the region of 5-H (δ 1.89) and 7-H (δ 3.93) signals when the signal of 11-H (δ 4.99) was irradiated, in contrast with the related compound **8a** with its ring B in a chair-like conformation, strongly suggest a twist-boat conformation for the ring B of tertiary alcohol **8c** and therefore a β orientation for the methyl group at C-8. The complete assignment of the ^1H NMR spectra of all compounds is in Table 2.

The twist-boat conformation of ring B of compounds **8c** and **9c**, and the chair-like conformation of **8a**, suggested on the basis of the spectral analysis discussed above, are in agreement with conformational calculations performed by the MMX[18] molecular mechanics program. The minimum-energy conformations of each compound are shown in Fig. 2. Furthermore, the calculated ^1H NMR coupling constants for 5-, 6- and 6-, 7-H for the ring B of compound **8c** in a twist-boat conformation ($J_{5\text{-H},6\text{-H}}$ 3.99, and $J_{6\text{-H},7\text{-H}}$ 8.17 Hz) in agreement with those experiment-

Table 2 ^{1}H NMR data for compounds **8a**, **8c**, **9a** and **9c**

	8a			**8c**			**9a**			**9c**		
	δ	Mult.	J (Hz)	δ	Mult.	J (Hz)	δ	Mult.	J (Hz)	δ	Mult.	J (Hz)
1-H	3.78	t	5.19	3.75	t	8.00	3.84	t	5.66	3.82	t	5.20
2-H$^\alpha$	1.82–1.90	m		1.88–2.00	overlapping	m	1.65–1.75	m		1.71	m	
2-H$^\beta$	1.60–1.75	m					1.85–1.92	m		1.85	m	
3-H$^\alpha$	1.42–1.50	m		1.35–1.50	overlapping	m	1.38–1.45	m		1.24	m	
3-H$^\beta$	1.25–1.35	m					1.20–1.35	m		1.42	m	
4-Me$^\alpha$	0.99	s		0.99	s		1.01	s		0.97*	s	
4-Me$^\beta$	1.06	s		1.07	s		0.98	s		0.99*	s	
5-H	1.61	d	1.87	1.89	d	2.00	2.04	d	10.44	2.10	d	10.66
6-H$^\alpha$	4.54	dd	6.24, 2.08	4.58	dd	2.00, 8.05						
6-H$^\beta$							4.34	dd	7.34, 11.0	4.34	dd	10.66, 7.34
7-H$^\alpha$	4.00–4.10	overlapping	m	3.93	d	8.05						
7-H$^\beta$							4.11	dd	3.36, 7.34	3.94	d	7.34
8-H	4.00–4.10	overlapping	m				4.19	dd	3.36, 6.12			
8-Me				1.34	s					1.25	s	
9-H	2.15	dd	4.10, 5.93	1.98	s		1.83	dd	6.00, 2.00	1.66	d	2.23
10-Me	1.37	s		1.41	s		1.06	s		1.06	s	
11-H	4.93	d	4.1	4.99	s		5.29	d	2.00	5.26	d	2.23
11-OMe	3.38	s		3.33	s		3.35	s		3.36	s	
Me, acetonide	1.32	s		1.30	s		1.48	s		1.47	s	
Me, acetonide	1.47	s		1.44	s		1.37	s		1.37	s	

* Assignments may be interchanged in each vertical row.

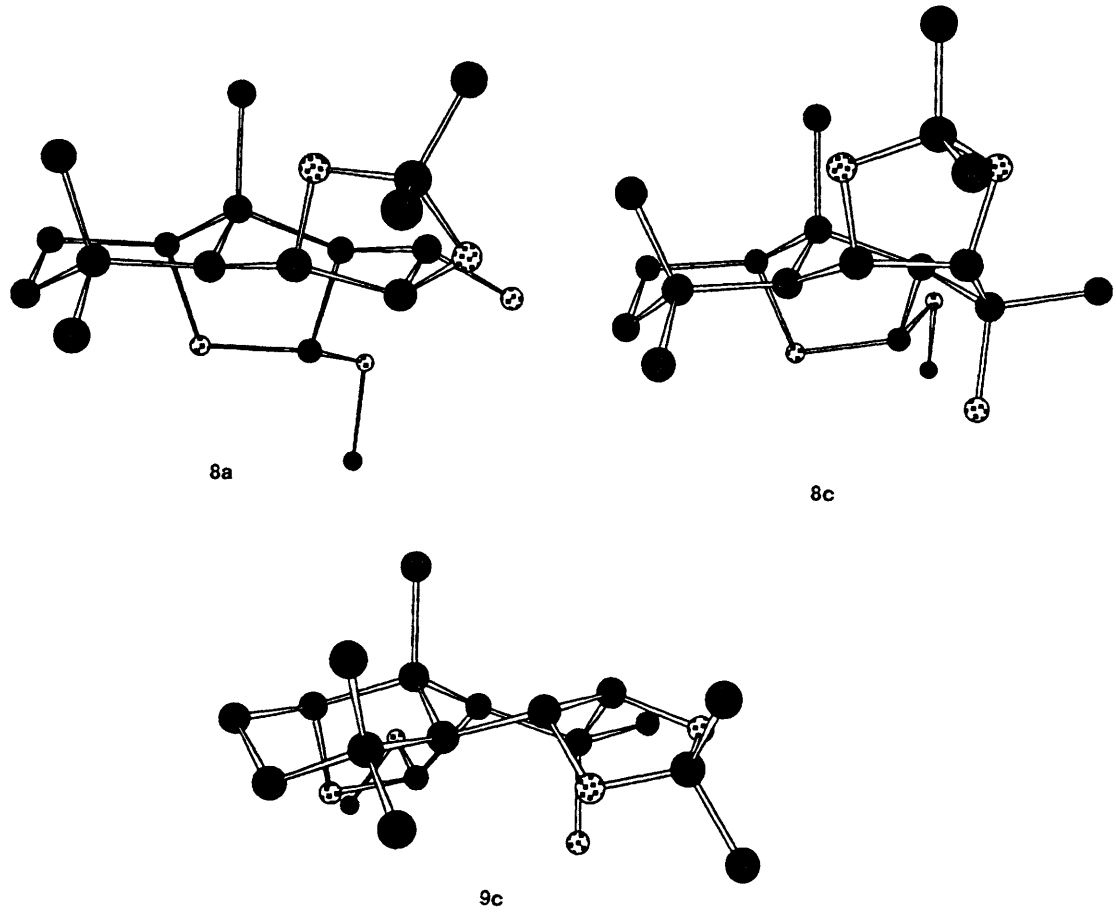


Fig. 2 Projections of the lowest-energy conformations of alcohols **8a**, **8c** and **9c** predicted on the basis of molecular mechanics calculations

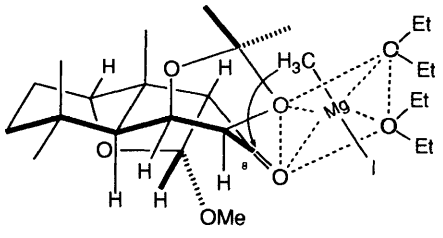


Fig. 3 Transition state for the addition reaction of MeMgI to ketone **8b** to give tertiary alcohol **8c**

ally observed ($J_{5\text{-H},6\text{-H}}$ 2.0, and $J_{6\text{-H},7\text{-H}}$ 8.05 Hz) were also supportive of the conformational assignment of this tertiary alcohol.

In conclusion, we have shown that the nucleophilic addition to the carbonyl group at C-8 of enone **7** and of the saturated ketone **10** occurs preferentially from the β-face of both molecules, but with different degrees of stereoselectivity depending upon the nature of both the substrate and the alkylating agent.

We have previously observed that the addition of methylmagnesium iodide and methyllithium to ketones **8b** and **9b**, respectively, occurred with a high degree of stereoselectivity.[6a] Now, in light of the results presented in this report, we can conclude that the stereochemistry at C-8 of the tertiary alcohols previously obtained are those of tertiary alcohols **8c** and **9c*** and therefore, that the nucleophilic additions had occurred from the β-face of both ketones. In the case of ketone **8b**, the addition is presumably through a chelate transition state as shown in Fig. 3,[19] for the most stable conformer of the starting ketone according to molecular mechanics calculations. We have also found that, in the allylic alcohol **11a**, the stereoselectivity of the osmylation reaction from the α-face of the molecule is greatly enhanced, allowing the development of an alternative sequence toward intermediate **4** *en route* to erigerol **2**.

* The stereochemistry at C-8 of **9c** was confirmed by X-ray analysis. We thank Dr. P. S. White for this determination.

Experimental

IR spectra were measured as solids in KBr disks, unless otherwise stated, in a Bruker FT-IFS25 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker 80 SY or a Bruker AC 200 spectrometer for $CDCl_3$ solutions with Me_4Si as internal standard. *J* Values are given in Hz. High-field measurements and 2D experiments were recorded on a Bruker AM 300 or AM 400 spectrometer as specified. For the 2D COSY and NOE experiments Bruker standard software was employed. Column chromatography was performed on silica gel 60 H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of EtOAc in hexane as solvent. Analytical TLC was carried out using Kielselgel Merck GF_{254} of thickness 0.20 mm. The homogeneity of all intermediates prior to the high-resolution mass spectral determination was carefully verified by TLC.

The numbering sequence used for reporting NMR parameters is illustrated in structure **7**.

General Procedures for the Preparation of Alcohols **11a** *and* **11b**.—*Method A* ($MeLi/MCl_3$). To anhydrous, vigorously stirred $CeCl_3$ [prepared from $CeCl_3 \cdot 7H_2O$ (426 mg, 1.14 mmol) according to Imamoto *et al.*[14]] in an ice-bath and under argon, was added anhydrous tetrahydrofuran (THF) (5.6 cm^3). The suspension was well stirred overnight under argon at room temperature or sonicated for 30 min.[20] To this stirred

suspension, maintained in an ice-bath, was added a 1.26 mol dm^{-3} solution of MeLi in Et_2O (3.8 cm^3), and the resulting orange mixture was stirred at 0 °C for 1.5 h. A solution of enone **7**[6a] (115 mg, 0.46 mmol) in THF (5 cm^3) was then added and after 15 min, when the TLC spot of the starting material had disappeared, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was poured into brine (30 cm^3) and extracted successively with Et_2O (2 × 25 cm^3) and EtOAc (2 × 15 cm^3). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The oily residue was shown to be a mixture of tertiary alcohols **11a** and **11b** as estimated by ^1H NMR spectroscopy. This viscous oil had δ_H(80 MHz) 0.88 (s, Me), 0.94 (s, Me), 0.99 (s, Me), 1.09 (s, Me), 1.33 (s, Me), 1.37 (s, Me), 3.44 (s, OMe), 3.45 (s, OMe), 4.00 (t, 1-H), 4.91 (d, *J* 6.02, 11-H), 5.34 (d, *J* 5.31, 11-H) and 5.50–6.07 (m, 6- and 7-H).

The reactions with $YbCl_3 \cdot 6H_2O$ were carried out under essentially the same reaction conditions; yields and ratios of products **11a** and **11b** are listed in Table 1.

Method B. To anhydrous, vigorously stirred $YbCl_3$ [prepared from $YbCl_3 \cdot 6H_2O$ (128 mg, 0.33 mmol) according to Utimoto *et al.*[15b]] in an ice-bath and under argon was added anhydrous THF (5 cm^3). The mixture was sonicated for 1 h at 0 °C.[20] To this stirred suspension, maintained in an ice-bath, was added a 3 mol dm^{-3} solution of MeMgBr in Et_2O dropwise (0.65 cm^3). Then, a cooled (0 °C) solution of enone **7**[6a] (55 mg, 0.22 mmol) in THF (6 cm^3) was added and the mixture was stirred. When the TLC spot of the starting material had disappeared (15 min), the reaction was quenched with saturated aq. NH_4Cl, and the mixture was poured into brine (30 cm^3) and extracted successively with Et_2O (2 × 25 cm^3) and EtOAc (2 × 15 cm^3). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. Yields and ratios of products **11a** and **11b** are listed in Table 1.

2aβ,3,4,5,5aα,6,7,8,8aβ,8b-*Decahydro*-2β-*methoxy*-6,6,8bβ-*trimethyl*-3-*oxo*-2H-*naphtho*[1,8-bc]*furan* **10**.—Enone **7**[6a] (151 mg, 0.64 mmol) was dissolved in MeOH (60 cm^3) and hydrogenated in the presence of 5% palladium on charcoal (44 mg) for 90 min at room temperature and 1 atm. After filtration of the catalyst through Celite, the filtrate was concentrated to dryness to afford *title compound* **10** as an oil that crystallized on storage (149 mg, 98%); δ_H(200 MHz) 0.88 (6 H, s, 2 × 4-Me), 1.20 (2 H, m, 3β- and 5-H), 1.27 (3 H, s, 10-Me), 1.54 (1 H, ddd, *J* 6.5, 11.0 and 13.3, 3α-H), 1.74–2.05 (4 H, m, 2- and 6-H_2), 2.30–2.70 (2 H, m, 7-H_2), 2.44 (1 H, d, *J* 3.20, 9-H), 3.40 (3 H, s, OMe), 3.95 (1 H, t, *J* 3.20, 1-H) and 5.07 (1 H, d, *J* 3.20, 11-H); δ_C(20 MHz) 81.90 (C-1), 21.37 (C-2), 34.88 (C-3), 32.43 (C-4), 31.50 (4-Me$^{\alpha}$), 20.04 (4-Me$^{\beta}$), 43.99 (C-5), 19.20 (C-6), 37.27 (C-7), 210.30 (C-8), 71.00 (C-9), 45.10 (C-10), 18.82 (10-Me), 105.13 (C-11) and 55.16 (OMe); *m/z* 252 (M^+) (Found: M^+, 252.1726. $C_{15}H_{24}O_3$ requires *M*, 252.1725).

General Procedures for the Preparation of Alcohols **12a** *and* **12b**.—The procedures were essentially identical with those for the preparation of compounds **11a** and **11b** described above. The product obtained was a mixture of tertiary alcohols as estimated by ^1H NMR spectroscopy. This viscous oil had δ_H(80 MHz) 0.80 (s, Me), 0.83 (s, Me), 0.89 (s, Me), 1.06 (s, Me), 1.22 (s, Me), 1.25 (s, Me), 1.33 (s, Me), 1.40 (s, Me), 3.40 (s, OMe), 3.43 (s, OMe), 3.88 (t, 1-H), 4.69 (d, *J* 6.31, 11-H) and 5.09 (d, *J* 5.67, 11-H). Yields and ratios of compounds **12a** and **12b** are listed in Table 1.

1,2,3,3aβ,5aβ,6,6aβ,9aβ,9bα,9c-*Decahydro*-6α-*hydroxy*-5β-*methoxy*-1,1,6β,8,8,9cβ-*hexamethyl*-5H-*furo*[4',3',2':4,5]-*naphtho*[1,2-d][1,3]*dioxolane* **9c**.—A mixture of osmium tetraoxide (72 mg, 0.28 mmol) in pyridine (0.5 cm^3) was slowly added to a stirred solution of the mixture of allylic alcohols **11a** and **11b** (50 mg, 0.19 mmol) in pyridine (1.0 cm^3) at 0 °C (entry 5 of Table 1). The brown solution was kept at this temperature for 1 h and was then warmed to room temperature. After being stirred for 12 h in the dark, the osmate ester was reduced by addition of THF (2.8 cm^3), water (0.8 cm^3), Celite (1.13 g) and solid $NaHSO_3$ (282 mg). The mixture was stirred vigorously at room temperature. When the reaction was complete as judged by TLC (3 h), the mixture was filtered through silica gel with copious washing (EtOAc). Concentration of the filtrate afforded a residue, which was dissolved in CH_2Cl_2 (50 cm^3). The resulting solution was washed successively with dil. HCl and saturated aq. $NaHCO_3$, dried (Na_2SO_4) and evaporated. The oily residue (41 mg) was used in the next step without further purification.

To a stirred solution of the crude mixture of triols (41 mg) in 2,2-dimethoxypropane (8.4 cm^3) was added a crystal of PTSA at room temperature. After 12 h, the reaction mixture was diluted with Et_2O (60 cm^3) and washed successively with saturated aq. $NaHCO_3$ and brine. After drying (Na_2SO_4) and removal of the solvent, the alcohol **9c** was obtained (35.8 mg, 56.5% overall from the mixture of substrates **11a** and **11b**), ν_{max}(KBr)/cm^{-1} 3540 (OH); δ_H see Table 2; δ_C(100 MHz) 81.91 (C-1), 22.58 (C-2), 35.00 (C-3), 32.14 (C-4), 32.50 (4-Me$^{\alpha}$), 23.99 (4-Me$^{\beta}$), 41.87 (C-5), 74.29 (C-6), 79.27 (C-7), 70.08 (C-8), 29.21 (8-Me), 64.90 (C-9), 44.15 (C-10), 23.78 (10-Me), 105.30 (C-11), 55.04 (OMe), 108.22 (OCO), 26.83 (Me, acetonide) and 22.74 (Me, acetonide); *m/z* 325 (M^+ − Me) (Found: M^+ − Me, 325.2011. $C_{18}H_{29}O_5$ requires *m/z*, 325.2015). These spectral data are coincident with those reported in ref. 6*a*.

Catalytic Hydrogenation of the Mixture of Alcohols **11a** *and* **11b**.—A 2:1 mixture of tertiary alcohols **11a** and **11b** (20 mg) was dissolved in EtOH (9 cm^3) and hydrogenated in the presence of PtO_2 (2.1 mg) for 90 min at room temperature and 1 atm. After filtration of the catalyst through Celite, the filtrate was evaporated to dryness. The ^1H NMR spectrum of the oily residue was similar to that described for the mixture of compounds **12a** and **12b**.

Preparation of β-*Hydroxy Sulfoximides* **14**.—To a stirred solution of *N,S*-dimethyl-*S*-phenylsulfoximide **13** (184.0 mg, 1.09 mmol) and triphenylmethane (7.5 mg) in anhydrous THF (15 cm^3) under argon and at 0 °C was added slowly a solution of MeLi (0.64 cm^3 of a 1.7 mol dm^{-3} solution in Et_2O, 1.09 mmol), and the resulting orange solution was allowed to warm to room temperature and was stirred for 15 min. The solution was then cooled to −78 °C and a solution of enone **7** (250 mg, 1.0 mmol) in THF (5 cm^3) was added slowly. When the TLC spot of the starting material had disappeared, the reaction mixture was allowed to warm to −20 °C and quenched with saturated aq. NH_4Cl. The mixture was poured into brine (30 cm^3) and extracted successively with Et_2O (2 × 25 cm^3) and EtOAc (2 × 15 cm^3). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to yield, after chromatography, the less polar β-hydroxy sulfoximides **14** as a foam (200.3 mg, 48%), ν_{max}(film)/cm^{-1} 3441, 1247, 1237, 1153 and 1104; δ_H(200 MHz) 0.87 (3 H, s, Me), 0.94 (6 H, s, 2 × Me), 1.10–1.85 (4 H, m, 2- and 3-H_2), 1.63 (1 H, d, *J* 4.40, 9-H), 2.30 (1 H, t, *J* 3.32, 5-H), 2.63 (3 H, s, NMe), 3.00 (1 H, d, *J* 13.70, C*H*HSONMePh), 3.42 (3 H, s, OMe), 3.43 (1 H, d, *J* 13.70, CH*H*SONMePh), 3.89 (1 H, t, *J* 3.20, 1-H), 5.45 (1 H, d, *J* 4.40, 11-H), 6.08 (1 H, dd, *J* 3.34 and 9.82, 6-H), 6.69 (1 H, dd, *J* 3.14 and 9.82, 7-H), 7.57–7.62 (3 H, m, Ar *m*-, *p*-H) and 7.89 (2 H, dd, *J* 1.50 and 7.48, Ar *o*-H); δ_C(20 MHz) 81.74 (C-1), 21.74 (C-2), 34.65 (C-3), 31.04 (C-4), 31.73 (4-Me$^{\alpha}$), 21.31 (4-Me$^{\beta}$), 42.25 (C-5), 133.18 (C-6), 129.83 (C-7), 69.51 (C-8), 66.06 (*C*H_2SONMePh), 28.65 (CH_2SO-N*Me*Ph), 138.81 (Ar), 131.48 (Ar), 129.51 (Ar), 129.03 (Ar),

67.81 (C-9), 48.73 (C-10), 19.61 (10-Me), 105.75 (C-11) and 55.64 (OMe).

The second product to elute was also a foam (119.6 mg, 28.5%), ν_{max}(film)/cm^{-1} 3441, 1241, 1151, 1108 and 1082; δ_H(200 MHz) 0.84 (3 H, s, Me), 0.93 (3 H, s, Me), 1.01 (3 H, s, Me), 1.10–1.85 (4 H, m, 2- and 3-H_2), 2.33 (1 H, t, *J* 3.04, 5-H), 2.66 (3 H, s, NMe), 2.88 (1 H, d, *J* 5.47, 9-H), 3.06 (1 H, d, *J* 13.98, C*H*HSONMePh), 3.34 (1 H, d, *J* 13.98, CH*H*SONMePh), 3.50 (3 H, s, OMe), 4.03 (1 H, t, *J* 3.04, 1-H), 5.43 (1 H, d, *J* 5.47, 11-H), 5.56 (1 H, dd, *J* 3.16 and 9.78, 7-H), 5.99 (1 H, dd, *J* 2.96 and 9.80, 6-H), 7.58–7.64 (3 H, m, Ar *m*-, *p*-H) and 7.90 (2 H, dd, *J* 1.5 and 7.6, Ar *o*-H); δ_C(20 MHz) 81.95 (C-1), 21.69 (C-2), 34.70 (C-3), 31.01 (C-4), 31.41 (4-Me$^{\alpha}$), 21.27 (4-Me$^{\beta}$), 42.06 (C-5), 132.95 (C-6), 129.97 (C-7), 69.88 (C-8), 64.60 (*C*H_2SONMePh), 28.44 (CH_2SON*Me*Ph), 139.52 (Ar), 131.62 (Ar), 129.32 (Ar), 128.66 (Ar), 61.85 (C-9), 47.91 (C-10), 18.72 (10-Me), 106.81 (C-11) and 55.54 (OMe).

Desulfurization of Sulfoximide **14**.—A solution of the less polar β-hydroxy sulfoximide (76.5 mg, 0.18 mmol) in absolute EtOH (12 cm^3) was stirred under reflux for 3 h in the presence of Raney nickel W-2 (5 cm^3 of the settled material) prepared according to ref. 21. The mixture was filtered through silica gel and the filter was washed (EtOH). Concentration of the filtrate afforded an oily residue that crystallized on storage (39.5 mg, 81%), δ_H(80 MHz) 0.80 (s, Me), 0.89 (s, Me), 1.06 (s, Me), 1.33 (s, Me), 3.43 (s, OMe), 3.88 (t, 1-H) and 5.09 (d, *J* 5.67, 11-H); δ_C(20 MHz) 82.87 (C-1), 21.78 (C-2), 35.60 (C-3), 32.24 (C-4), 31.96 (4-Me$^{\alpha}$), 21.18 (4-Me$^{\beta}$), 44.82 (C-5), 18.47 (C-6), 38.80 (C-7), 70.06 (C-8), 31.55 (8-Me), 67.63 (C-9), 43.99 (C-10), 19.71 (10-Me), 106.73 (C-11) and 55.78 (OMe). These spectral data are coincident with those described for compound **12a**. The same result was obtained when the more polar β-hydroxy sulfoximide was submitted to the reaction conditions described above.

1,2,3,3aβ,5aβ,6,6aα,9aα,9bα,9c-*Decahydro*-6α-*hydroxy*-5β-*methoxy*-1,1,6β,8,8,9cβ-*hexamethyl*-5H-*furo*[4′,3′,2′:4,5]*naphtho*[1,2-d][1,3]*dioxolane* **8c**.—A solution of the less polar β-hydroxy sulfoximide **14** (46.6 mg, 0.11 mmol) in THF (0.35 cm^3) was added to a stirred solution of osmium tetraoxide (31 mg, 0.12 mmol) and pyridine (0.02 cm^3, 0.26 mmol) in THF (4.2 cm^3) at 0 °C and the mixture was then warmed to room temperature. After being stirred for 93 h, the osmate ester was reduced by addition of THF (1.22 cm^3), water (0.37 cm^3), Celite (487 mg) and solid $NaHSO_3$ (122 mg). The mixture was stirred vigorously at room temperature for 11 h and was then filtered through silica gel with copious washing (EtOAc). Concentration of the filtrate afforded a residue (38.9 mg), which was used in the next step without further purification.

To a stirred solution of the crude product in 2,2-dimethoxypropane (0.6 cm^3) was added a crystal of PTSA at room temperature. After 21 h, the reaction mixture was diluted with Et_2O and washed successively with saturated aq. $NaHCO_3$ and brine. After drying (Na_2SO_4) and removal of the solvent, the residue (40.2 mg) was chromatographed to give compound **15** (11.1 mg, 26%) as an oil, δ_H(200 MHz) 1.04 (3 H, s, 4α-Me), 1.08 (3 H, s, 4β-Me), 1.28 (3 H, s, Me, acetonide), 1.40 (3 H, s, 10-Me), 1.44 (3 H, s, Me, acetonide), 1.50 (2 H, m, 3-H_2), 1.70 (1 H, s, 9-H), 1.92 (2 H, m, 2-H_2), 2.02 (1 H, d, *J* 2.16, 5-H), 2.58 (3 H, s, NMe), 3.25 (1 H, d, *J* 13.70, C*H*HSONMePh), 3.28 (3 H, s, OMe), 3.43 (1 H, d, *J* 13.70, CH*H*SONMePh), 3.74 (1 H, t, *J* 6.98, 1-H), 4.66 (1H, dd, *J* 2.16 and 8.24, 6-H), 4.77 (1 H, d, *J* 8.24, 7-H), 5.10 (1 H, s, 11-H), 7.57–7.62 (3 H, m, Ar *m*-, *p*-H) and 7.89 (2 H, dd, *J* 1.50 and 7.48, Ar *o*-H); δ_C(50 MHz) 85.93 (C-1), 23.67 (C-2), 35.00 (C-3), 32.08 (C-4), 30.83 (4-Me$^{\alpha}$), 26.47 (4-Me$^{\beta}$), 39.28 (C-5), 72.67 (C-6), 76.08 (C-7), 72.17 (C-8), 59.91 (*C*H_2SONMePh), 28.76 (CH_2SON*Me*Ph), 138.53 (Ar), 133.10 (Ar), 129.49 (Ar), 128.93 (Ar), 61.94 (C-9), 42.71 (C-10), 27.50 (10-Me), 106.01 (C-11), 54.08 (OMe), 107.87 (OCO), 25.43 (Me, acetonide) and 22.83 (Me, acetonide).

A solution of compound **15** (11.1 mg, 0.02 mmol) in absolute EtOH (10 cm^3) was hydrogenated in the presence of Raney nickel W-2 (0.64 cm^3 of the settled material), prepared according to ref. 21, for 17 h at room temperature and 1.5 atm. After filtration of the catalyst through Celite, the filtrate was concentrated to dryness to afford compound **8c** as an oil (8.2 mg, 100%), ν_{max}(KBr)/cm^{-1} 3490; δ_H see Table 2; δ_C(100 MHz) 85.76 (C-1), 23.89 (C-2), 34.67 (C-3), 32.03 (C-4), 30.56 (4-Me$^{\alpha}$), 26.95 (4-Me$^{\beta}$), 39.55 (C-5), 72.83 (C-6), 80.12 (C-7), 70.41 (C-8), 27.86 (8-Me), 59.82 (C-9), 41.97 (C-10), 28.04 (10-Me), 106.28 (C-11), 54.33 (OMe), 107.85 (OCO), 22.95 (Me, acetonide) and 25.83 (Me, acetonide); *m*/*z* 340 (M^+) (Found: M^+, 340.2245. $C_{19}H_{32}O_5$ requires *m*/*z*, 340.2250). These spectral data are coincident with those reported in ref. 6*a*.

Acknowledgements

We thank CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) and UNR (Universidad Nacional de Rosario) for financial support and fellowships (J. A. B., M. D. P.).

References

1 S. V. Bhat, B. S. Bajwa, H. Dornauer, N. J. de Souza and H.-W. Fehlhaber, *Tetrahedron Lett.*, 1977, 1669.
2 For a review on synthetic routes to forskolin, see M. I. Colombo, J. Zinczuk and E. A. Rúveda, *Tetrahedron*, 1992, **48**, 963.
3 K. B. Seamon and J. W. Daly, *Adv. Cyclic Nucleotide Protein Phosphorylation Res.*, 1985, **20**, 1; Y. Khandelwal, K. Rajeshwari, R. Rajagopalan, L. Swamy, A. N. Dohadwalla, N. J. de Souza and R. H. Rupp, *J. Med. Chem.*, 1988, **31**, 1872; S. L. Schreiber, *Chem. Eng. News*, 1992, **70**, (43), 22.
4 T. G. Waddell, C. B. Osborne, R. Collison, M. J. Levine, M. C. Cross, J. V. Silverton, H. M. Fales and E. A. Sokoloski, *J. Org. Chem.*, 1983, **48**, 4450.
5 C. Somoza, M. I. Colombo, A. C. Olivieri, M. Gonzalez-Sierra and E. A. Rúveda, *Synth. Commun.*, 1987, **17**, 1727; F. Kienzle, J. Stadlwieser, W. Rank and P. Schönholzer, *Helv. Chim. Acta*, 1990, **73**, 1108.
6 (*a*) M. I. Colombo, J. Zinczuk, J. A. Bacigaluppo, C. Somoza and E. A. Rúveda, *J. Org. Chem.*, 1990, **55**, 5631; (*b*) J. A. Bacigaluppo, M. I. Colombo, J. Zinczuk and E. A. Rúveda, *Synth. Commun.*, 1992, **22**, 1973.
7 For a review on the application of lanthanide reagents in organic synthesis, see G. A. Molander, *Chem. Rev.*, 1992, **92**, 29.
8 A. S. Gupta, S. Dev, M. Sangaré, B. Septe and G. Luckas, *Bull. Soc. Chim. Fr.*, 1976, 1879.
9 C. R. Johnson and M. R. Barbachyn, *J. Am. Chem. Soc.*, 1984, **106**, 2459.
10 C. R. Johnson and C. J. Stark Jr., *J. Org. Chem.*, 1982, **47**, 1193.
11 C. R. Johnson, *Aldrichim. Acta*, 1985, **18**, 3.
12 M. D. Preite, J. Zinczuk, M. I. Colombo, J. A. Bacigaluppo, M. González-Sierra and E. A. Rúveda, *Tetrahedron Asymm.*, 1993, **4**, 17.
13 J. A. Bacigaluppo, M. I. Colombo, J. Zinczuk, S. N. Huber, M. P. Mischne and E. A. Rúveda, *Synth. Commun.*, 1991, **21**, 1361.
14 T. Imamoto, M. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392.
15 (*a*) G. A. Molander, E. R. Burkhardt and P. Weinig, *J. Org. Chem.*, 1990, **55**, 4990; (*b*) K. Utimoto, A. Nakamura and S. Matsubara, *J. Am. Chem. Soc.*, 1990, **112**, 8189.
16 J. H. Noggle and R. F. Schirmer, *The Nuclear Overhauser Effect*, Academic Press, New York, 1971, p. 44; M. L. Martin, J.-J. Delpuech and G. J. Martin, *Practical NMR Spectroscopy*, Heyden, London, 1980, p. 199.
17 R. Bucourt, *Top. Stereochem.*, 1974, **8**, 159.
18 N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, 1973, **95**, 3893.
19 T. K. M. Shing, H. Tsui, Z. Zhou and T. C. W. Mak, *J. Chem. Soc., Perkin Trans. 1*, 1992, 887; J. G. Buchanan, M. L. Quijano and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1573.
20 N. Greeves and L. Lyford, *Tetrahedron Lett.*, 1992, **33**, 4759.
21 R. Mozingo, *Org. Synth.*, 1955, Coll. Vol. 3, p. 181.

Paper 3/01786I
Received 6*th April* 1993
Accepted 11*th May* 1993