A New Protocol for Regio- and Stereocontrolled Aldol Reactions through the Conjugate Addition of Dialkylboranes to α,β-Unsaturated Ketones[1]

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Received February 11, 1991

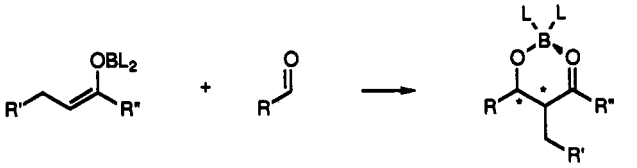
A one-pot, two-step procedure, consisting of the 1,4-addition of dialkylboranes to β-substituted (*E*)-α,β-unsaturated ketones followed by the reaction of the resulting configurationally pure (*Z*)-(vinyloxy)boranes with aldehydes, is reported. The overall process corresponds to a regio- and stereocontrolled aldol addition of an unsymmetrical ketone to an aldehyde. A concerted 1,4-addition mechanism accounts for the stereochemical outcome of the hydroboration reaction; cyclic enones do not undergo conjugate addition, while (*Z*)-β-substituted or β,β-disubstituted α,β-unsaturated ketones still react in a 1,4-fashion, but with a slower rate and a lower degree of chemoselectivity with respect to β-substituted (*E*)-α,β-unsaturated ketones. In the cases of α,β-disubstituted α,β-unsaturated ketones and (*E*)-(*S*-phenylthio)cinnammate, which react with dicyclohexylborane to give a mixture of *E* and *Z* enolates, an alternative mechanism is proposed.

Introduction

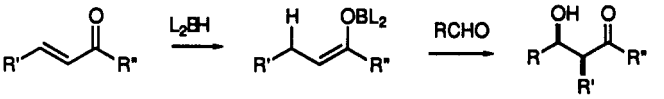
Boron enolates are uniquely useful reagents for directed stereocontrolled aldol reactions (Scheme I).[2] Depending on the nature of ligands L, we refer to enolborinates (or (vinyloxy)boranes) (L = alkyl) or to enolborates (or (vinyloxy)boronates) (L = alkoxy). In comparison with aldol reactions involving enolates of other metals, the short B–O bond length (1.36–1.47 Å) and the acceptor properties of the tricoordinated boron atom favor, in the case of boron enolates, the formation of tightly closed transition-state structures where steric effects among substituents are magnified, and stereocontrol is enhanced.[3] The closed transition-state hypotheses were recently confirmed by theoretical calculations at various computational levels and accuracies.[4]

The classical route to boron enolates involves the enolization of a carbonyl compound with an amine in the presence of a suitable borylating agent L_2BX (X = Cl, CF_3SO_2, etc.).[2,3] The regiochemistry of this process, in the case of unsymmetrical ketones, is acceptably controlled only in few particular cases. On the other hand, the enolate configuration can be more easily controlled through a proper choice of the reaction conditions, the base, and the boron substituents L and X.[2c,3j]

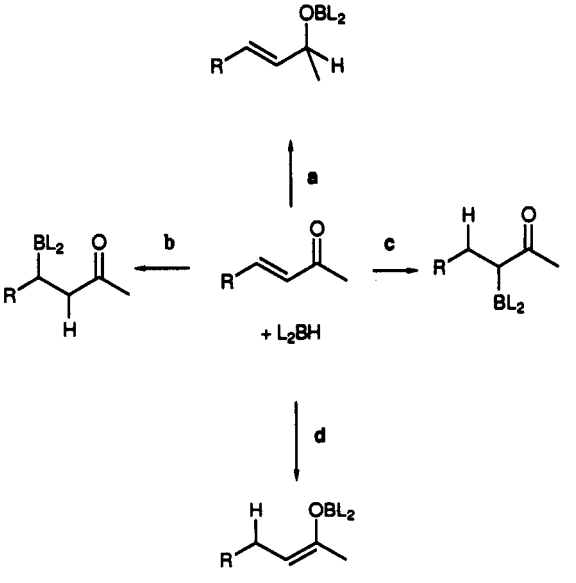
Scheme I



Scheme II



Scheme III



A main goal pursued by us in recent years has been the development of indirect routes to regio- and stereochemically defined boron enolates formally deriving from unsymmetrical ketones. For example, we carried out regio-, diastereo-, and enantioselective condensation reaction of butanone with aldehydes.[5] The required configurationally

(1) Initial presentation of results at the 8th IUPAC Conference on Organic Synthesis, Helsinki, Finland, July 23, 1990, and at the Congresso Interdivisionale della Società Chimica Italiana CISCI '90, S. Benedetto del Tronto, Italy, Sept 30, 1990.

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(3) (a) Fenzl, W.; Koester, R. *Liebigs Ann. Chem.* **1975**, 1322. (b) Masamune, S.; Mori, S.; Van Horn, D., Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. (c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. (d) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (e) Evans, D. A.; Bartroli, J.; Shih, T. L. *Ibid.* **1981**, *103*, 2127. (f) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *Ibid.* **1981**, *103*, 1566. (g) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *Ibid.* **1986**, *108*, 8279. (h) Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721. (i) Enders, D.; Lohray, B. B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 581. (j) Brown, H. C.; Dhar, R. K., Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441. (k) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *Ibid.* **1989**, *111*, 5493. (l) Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* **1989**, *54*, 2817. (m) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767.

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0022-3263/91/1956-5820$02.50/0

Table I. Conjugate Addition of Dialkylboranes to (*E*)-α,β-Enones

entry	borane	α,β-enone	solvent	T (°C)	t (h)	saturated ketone[a] (%)	allylic alcohol[a] (%)
1	Sia_2BH	4-hexen-3-one	$CDCl_3$	0 → 20	4	92	0.5
2	Chx_2BH	4-hexen-3-one	$CDCl_3$	0 → 20	0.5	90	0.4
3	Ipc_2BH	4-hexen-3-one	$CDCl_3$	0 → 20	2	88	0.5
4	Icr_2BH	4-hexen-3-one	$CDCl_3$	0 → 20	1.5	92	0.2
5	9-BBN	4-hexen-3-one	$CDCl_3$	0 → 20	8	52	23
6	Ipc_2BH	4-phenyl-3-buten-2-one	THF	20	1	92	3.6
7	9-BBN	4-phenyl-3-buten-2-one	$CDCl_3$	0 → 20	8	33	50
8	CatBH	4-phenyl-3-buten-2-one	THF	20	3	51	7.2
9	Ipc_2BH	β-ionone	CD_2Cl_2	20	3	86	0.9
10	Ipc_2BH	1,3-diphenylpropenone	THF	20	3	88	4.2
11	Chx_2BH	1,3-diphenylpropenone	CD_2Cl_2	20	3	85	3.8

[a] Product yields were determined by capillary GC analysis. See Experimental Section.

pure (*E*)- and (*Z*)-(vinyloxy)boronates contained the tartaric acid framework as chiral auxiliary and were prepared upon oxidation of vinylboronates with trimethylamine oxide.

More recently, we reported an unprecedented route to boron enolates from the 1,4-hydroboration reaction of β-substituted (*E*)-α,β-unsaturated ketones with diisopinocampheylborane (Ipc_2BH) or dicyclohexylborane (Chx_2BH), which affords configurationally pure (*Z*)-(vinyloxy)boranes.[6] The following reaction with aldehydes gives virtually pure syn aldols (Scheme II).

Using 4-hexen-3-one as model substrate, we also observed that the same reactivity is shared by other representative dialkylboranes such as disiamylborane (Sia_2BH), di-2-isocaranylborane (Icr_2BH), and, in part, by borabicyclononane (9-BBN).[7] In the meantime, a related conjugate reduction of α,β-unsaturated ketones by catecholborane (CatBH) was independently reported by Evans.[8] Such a behavior exhibited by dialkylboranes was unexpected since 9-BBN was commonly considered a chemoselective reducing agent for the transformation of α,β-unsaturated ketones into allylic alcohols.[9] The most attractive feature of the 1,4-hydroboration of α,β-unsaturated ketones is given by the fact that it represents a simple and unambiguous approach to a single boron enolate among the four regio- and stereoisomeric enolates that can be obtained from the enolization of a typical unsymmetrical ketone such as 3-hexanone.

Results

The hydroboration of an α,β-unsaturated ketone might take place according to four reaction mechanisms (Scheme III).[10] Route **a** represents the 1,2-addition of the borane to the C=O bond;[9] routes **b** and **c** are the two regioisomeric 1,2-addition reactions to the C=C bond and have been proposed in order to account for the reduction of α,β-unsaturated esters with Sia_2BH[11] and 9-BBN,[12] finally, **d** is the 1,4-conjugated addition to the α,β-unsaturated carbonyl compounds.

Depending on the characteristics of the substrate and of the borane, one or more mechanisms are followed. For example, all the boranes examined in this work show a sharp preference for the C=O reduction of cyclohexenone. Moving to open-chain α,β-unsaturated ketones, the presence of one or more substituents in the α and β positions can favor different reduction pathways.

The simplest unsubstituted enone, methyl vinylketone, reacts in a few minutes with both Chx_2BH and Ipc_2BH to give, after oxidative workup (H_2O_2), a plethora of products deriving from single and double hydroboration reactions. If the reaction is carried out with (−)-Ipc_2BH at a temperature rising from −30 to 0 °C in 1.5 h and then benzaldehyde is added,[13] *syn*-(3*S*,4*S*)-4-hydroxy-3-methyl-4-phenylbutan-2-one is found in 18% yield and 23% ee, as established by comparing the optical rotation value $[\alpha]^{20}_D$ −11.8° (*c* 1.06, $CHCl_3$) with the literature value.[5] This result allowed us to ascertain that, among the various borylated intermediates, there was a single (vinyloxy)borane with *Z* configuration and confirmed the preference of the Ipc_2B-enolates deriving from (+)-α-pinene for an attack to the *si* face of the aldehyde, as reported by Paterson.[2c]

Moving to β-monosubstituted ketones, we found that the chemoselectivity of the hydroboration process is affected by the geometry of the C=C bond. In fact, in the case of (*E*)-α,β-unsaturated ketones, the 1,4-addition becomes the dominant process. In Table I we report a set of experiments aimed at determining the chemoselectivity of the hydroboration reaction of some representative (*E*)-β-monosubstituted α,β-unsaturated ketones. Aliquots of the reaction mixture were quenched with water,[14] and the amounts of saturated ketone and allylic alcohol were determined by GC analysis.

The chemoselectivity of the conjugate addition reaction, expressed by the ratio saturated ketone/allylic alcohol, reaches very high levels ranging from 460:1 (entry 4) to 21:1 (entry 10), with the exception of CatBH (entry 8) and, particularly, 9-BBN (entries 5 and 7), which gives high levels of C=O reduction.[9] Several experiments listed in Table I were carried out in deuterated solvents in order

(6) Boldrini, G. P.; Mancini, F.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1680.
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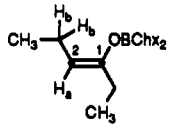
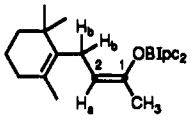
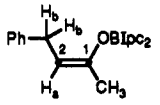
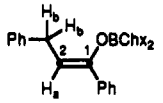
(8) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678.
(9) Krishnamurti, S.; Brown, H. C.; *J. Org. Chem.* **1977**, *42*, 1197.
(10) We do not consider the possibility of a nucleophilic attack of hydride to the α,β-unsaturated ketone, since dialkylboranes do not act in general as hydride donors. Typical hydride donors are quaternary hydroborate species like L-Selectride (Aldrich), which reduces α,β-unsaturated ketones to give boron enolates through a formal conjugate addition. In this case, the geometry of the enolate can be predicted on the basis of the ground-state conformational preference of the ketone. For example, ketones mainly existing as s-trans conformers are converted by L-Selectride to (*E*)-(vinyloxy)boranes; see: Chamberlin, A. R.; Reich, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 1440. It is interesting to notice that the same ketones give, when treated with dialkylboranes, the opposite configuration, namely (*Z*)-(vinyloxy)boranes.
(11) Brown, H. C.; Keblys, K. A. *J. Am. Chem. Soc.* **1964**, *86*, 1795.
(12) Brown, H. C.; Chen, J. C. *J. Org. Chem.* **1981**, *46*, 3978.
(13) When the same experiment was carried out at −78 °C no condensation product was isolated.
(14) Quenching with D_2O the reaction corresponding to entry 9 afforded α-deuterio-β-ionone identified by MS: *m/z* 195 (M^+ 5), 177 (17), 162 (34), 136 (M^+ − $CHDCOCH_3$, 27), 121 (100), 107 (21), 93 (44), 43 (95). Aliquots of various reaction mixtures were also quenched with H_2O_2 in pH 7 buffered solutions; we never detected α- or β-hydroxy ketones.

Table II. Selected NMR Data of Boron Enolates[a]

boron enolate	δ H_a (mult)	δ H_b (mult)	$J_{a,b}$ (Hz)	δ C_1	δ C_2
 1	4.58 (tt)[b]	1.86 (t quintet)[c]	7.0	152.5	109.7
 2	4.52 (t)	2.56 (d)	6.8	147.3	111.0
 3	4.70 (tq)[b]	3.07 (d)	7.3	149.5	109.2
 4	5.70 (t)	3.44 (d)	7.4	150.2	109.4

[a] NMR spectra were taken on a Varian Gemini-300 instrument in $CDCl_3$ (enolates 1 and 3) or CD_2Cl_2 (enolates 2 and 4). The *E* boron enolate, if present, has to be in concentration below the instrumental limit of detection. [b] A 1.1-Hz allylic coupling constant is observed. [c] A 1.1-Hz homoallylic coupling constant is observed.

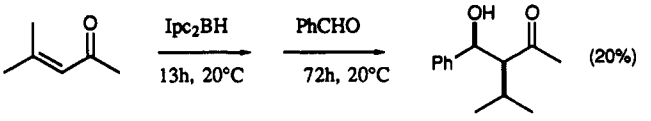
to record the NMR spectra of the hydroboration mixtures. The low-field region of both ^1H and ^{13}C NMR spectra reveals single sets of signals that are distinctive of (vinyloxy)boranes with *Z* configuration. The data of four representative (vinyloxy)boranes are reported in Table II.

The 1.1-Hz allylic coupling constants observed in entries 1 and 3 are known to be typical of (*Z*)-(vinyloxy)boranes;[2c,3a] moreover, NOE experiments gave positive enhancements (1–5%) of ethyl and methyl multiplets in cis arrangement with respect to the irradiated H_a hydrogen in entries 1–3. Only in the case of the 9-BBN-derived (vinyloxy)borane (entry 5 of Table I) a triplet at 4.73 ppm (J = 7.7 Hz) corresponding to the *E* enolate is present together with the triplet of triplets at 4.63 ppm of the *Z* enolate in a 1:5 ratio.[7] This observation confirms the known behavior of 9-BBN enolates that easily undergo *Z*–*E* equilibration.[15]

Considering that a new straightforward route to regio- and stereodefined (vinyloxy)boranes is available, a simple and practical one-pot aldol condensation protocol has been worked out. It consists of two steps, the hydroboration step and the condensation step, the latter carried out by simply pouring the aldehyde into the hydroboration mixture. The results of the corresponding reductive condensations of (*E*)-α,β-enones with aldehydes are collected in Table III.

The most important feature of this aldol condensation process is given by the very high level of diastereoselectivity exhibited, the >95% syn purity of the resulting ketols (by the limits of detection by ^1H NMR spectroscopy) being the consequence of the stereoselectivity of the hydroboration step, which affords virtually pure (*Z*)-(vinyloxy)boranes. Even though the reaction conditions were not optimized, the overall yields, corresponding to the isolated ketols, and the easiness of the experimental procedure appear quite attractive from a synthetic point of view. The enantioselectivities, when (–)-Ipc_2B enolates are used, fit those reported by Paterson for similar enolates;[2c] we also confirmed that α-branched saturated aldehydes (entry 9) give poorer results than linear or aromatic aldehydes. The lack of self-condensation products when enolizable aldehydes are used (entries 5, 8) and of dehydration products is also worth mentioning.

Scheme IV

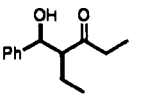
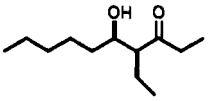
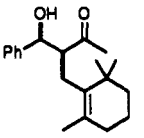
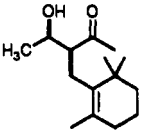
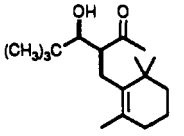
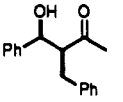
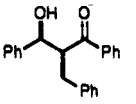


Considering that, among the experiments listed in Table III, the best chemical and optical yields were obtained using (*E*)-4-phenyl-3-buten-2-one (entry 10), we decided to study the effect of inverting the substrate configuration. We found that, under the same experimental conditions, (*Z*)-4-phenyl-3-buten-2-one reacts with Ipc_2BH in THF and $CHCl_3$ much more slowly (~28% conversion after 2 h at 20 °C) and with a lower chemoselectivity; in fact, the saturated ketone/allylic alcohol ratio was 2:1 vs 25:1 given by (*E*)-4-phenyl-3-buten-2-one (entry 6 of Table I). Anyway, when a hydroboration reaction was carried out with (–)-Ipc_2BH in $CDCl_3$ for 5 h we did not detect signals due to the *E* enolate but only the same triplet of quartets characteristic of the *Z* enolate 3 of Table II. Quenching the reaction with benzaldehyde afforded, after 16 h at –30 °C, *syn*-4-hydroxy-4-phenyl-3-(phenylmethyl)-2-butanone in 32% yield and 66% e.e. An analogous slow hydroboration rate was observed using 4-methyl-3-penten-2-one and Chx_2BH in THF (Scheme IV). After 13 h at 20 °C only 50% of the starting enone had reacted; benzaldehyde was added to this mixture, and again the syn ketol was the sole condensation product isolated in 40% yield, based the reacted enone.

Finally, we examined two substrates that gave very different results in terms of mechanistic preference of the hydroboration reaction. The first substrate is a typical α,β-disubstituted enone, namely (*E*)-3-methyl-3-penten-2-one. When it was allowed to react with Chx_2BH in $CDCl_3$ at 20 °C for 1 h, the ^{13}C NMR spectrum of the reaction mixture showed two pairs of signals attributed to vinylic carbons: at 141.7 and 118.1 ppm for the major

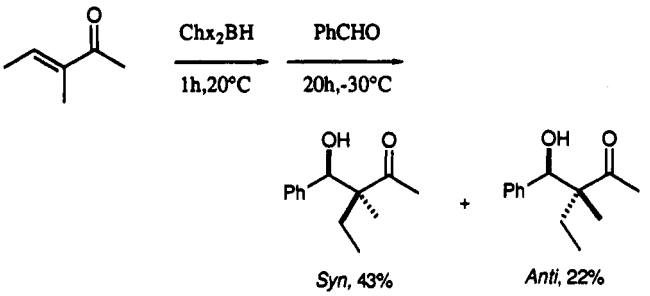
(15) See ref 2a, p 134.

Table III. Reductive Condensations of (*E*)-α,β-Enones with Aldehydes[a]

entry	borane	α,β-enone	aldehyde	solvent	condensation parameters: *T* (°C)	*t* (h)	product	yield[b] (%)	ee[c] (%)
1	Sia_2BH	4-hexen-3-one	PhCHO	$CHCl_3$	0	16		62	
2	Chx_2BH	4-hexen-3-one	PhCHO	$CHCl_3$	20	4		57	
3	Ipc_2BH	4-hexene-3-one	PhCHO	$CHCl_3$	−40	10		65	64
4	Icr_2BH	4-hexen-3-one	PhCHO	$CHCl_3$	0	20		83	31[d]
5	Ipc_2BH	4-hexen-3-one	Hexanal	THF	−50	24		54	65
6	Ipc_2BH	β-ionone	PhCHO	THF	−30	16		77	75
7	Ipc_2BH	β-ionone	PhCHO	CH_2Cl_2	−60	2.5		70	62
8	Ipc_2BH	β-ionone	CH_3CHO	THF	−30	16		60	75
9	Ipc_2BH	β-ionone	$(CH_3)_3CCHO$	THF	20	40		30	50
10	Ipc_2BH	4-phenyl-3-buten-2-one	PhCHO	THF	−70[e]	10		91	90
11	Ipc_2BH	1,3-diphenylpropenone	PhCHO	THF	−70	15		80	60
12	Chx_2BH	1,3-diphenylpropenone	PhCHO	$CHCl_3$	−30	17		77	

[a] The hydroboration is always carried out by poruing the enone into a slurry or solution of the borane in the reported solvent at 0 °C and then stirring for 2 h at room temperature. [b] Yields refer to the overall two-step process and are determined on the pure isolated ketol. [c] Determined by ^1H NMR analysis of the corresponding Mosher's esters. [d] In this experiment Icr_2BH was prepared from (+)-2-carene and afforded the (−)-ketol: $[\alpha]^D_{20}$ −9.2 (*c*, 1.0 in $CHCl_3$). [e] After 10 h the temperature was allowed to rise to −30 °C.

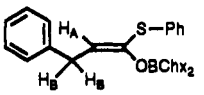
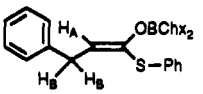
Scheme V



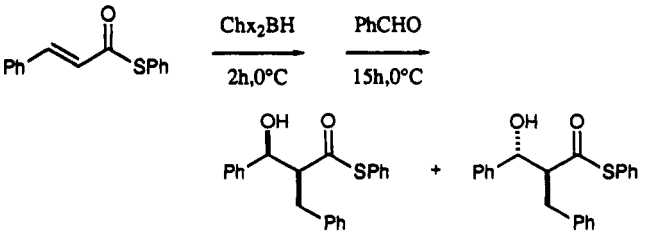
isomer and at 138.7 and 115.8 for the minor isomer in a 2:1 ratio. The existence in this case of two (vinyloxy)boranes was confirmed by the following condensation reaction. In fact, after addition of benzaldehyde we detected two diastereomeric products, the syn and the anti ketol shown in Scheme V, in a 2:1 ratio.

An analogous result was obtained when an (*E*)-α,β-unsaturated thioester, namely (*E*)-4-phenyl-3-propenethioic acid, *S*-phenyl ester, was allowed to react with Chx_2BH in $CDCl_3$. Both *E* and *Z* enolates in a 1:1 ratio were detected by ^1H NMR analysis; their characteristic signals are reported in Table IV. The reaction with benzaldehyde gave two β-hydroxy thioesters in the 3:4 ratio (Scheme VI).

Table IV

enolate	δ H_A (mult)	δ H_B (mult)	$J_{A/B}$ (Hz)
	5.53 (t)	3.70 (d)	7.9
	5.63 (t)	3.43 (d)	7.4

Scheme VI



Discussion

The hypothesis we made[1,6,7] in order to account for the high stereoselectivity of the hydroboration reaction of

Scheme VII

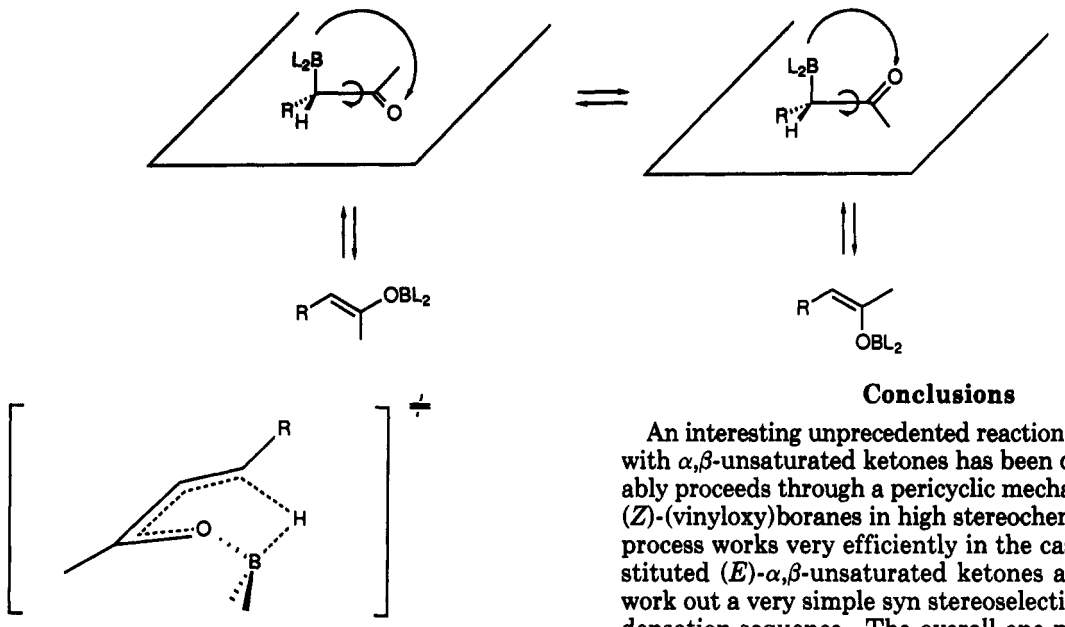


Figure 1.

β-substituted (*E*)-α,β-unsaturated ketones assumes that a concerted pericyclic [4π + 2σ] mechanism is followed when an s-cis conformation can be adopted by the enone. The s-cis conformation is readily accessible in the case of disubstituted (*E*)-α,β-unsaturated ketones since it represents a relative minimum-energy conformation with a low energy barrier for the conversion to the more stable s-trans conformation.[16] The *Z* configuration of the resulting (vinyloxy)borane reflects the s-cis arrangement of the enone in the transition-state structure proposed in Figure 1.

If the adoption of an s-cis conformation is essential in order to make the concerted 1,4-addition pathway possible, it is easy to anticipate that substituents on the β carbon in cis relationship with respect to the carbonyl group (e.g., (*Z*)-4-phenyl-3-buten-2-one and 4-methyl-3-penten-2-one) or on the α-carbon (e.g., (*E*)-3-methyl-3-penten-2-one) will slow down the reaction by destabilizing the planar conformation required by the pericyclic transition state. As a consequence, mechanisms a–c of Scheme III become competitive with d and the chemoselectivity of the hydroboration process gets low. There is an interesting difference in the behavior of β-cis- and α-substituted enones examined: the former type of ketones gives a single (*Z*)-(vinyloxy)borane together with borylated allylic alcohols deriving from C=O reduction; the second gives a mixture of *E* and *Z* enolates, as (*E*)-4-phenyl-3-propenethioic acid, *S*-phenyl ester does. The lack of stereoselectivity observed in these last two cases can be the result of two different processes: (i) the (*Z*)-(vinyloxy)borane produced through the concerted mechanism is not configurationally stable and undergoes *Z*–*E* equilibration;[17] (ii) the second hypothesis involves the 1,2-hydroboration of the C=C bond (Scheme III, path c) to give the α-borylated ketone, which rearranges to the more stable (*E*)- and (*Z*)-(vinyloxy)boranes (the B–O bond is stronger than the B–C bond by 30–40 kcal/mol when boron is tricoordinate), as shown in Scheme VII.

(16) Lilyefors, T.; Allinger, N. L. *J. Am. Chem. Soc.* **1976**, *98*, 2745.
(17) A process similar to the *Z*–*E* isomerization of crotylboranes could take place; see: Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564.

Conclusions

An interesting unprecedented reaction of dialkylboranes with α,β-unsaturated ketones has been disclosed; it probably proceeds through a pericyclic mechanism and affords (*Z*)-(vinyloxy)boranes in high stereochemical purity. The process works very efficiently in the case of β-monosubstituted (*E*)-α,β-unsaturated ketones and allowed us to work out a very simple syn stereoselective reductive condensation sequence. The overall one-pot, two-step procedure is particularly valuable when it affords aldols formally deriving from unsymmetrical ketones and aldehydes. In fact, the standard enolization techniques do not allow to synthesize regiochemically defined enolates starting, for example, from 3-hexanone.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, in $CDCl_3$. Low-resolution mass spectra (MS) were measured at 70 eV. GC analyses were performed using a 30-m capillary Supelcowax column (film thickness 0.35 μm) with hydrogen as carrier gas. Analytical TLC was performed by using Kieselgel 60 F_{254} plates. Flash chromatography was performed by using Kieselgel 60 (230–400 mesh). All operations were carried out under Ar, with oven-dried glassware; all solvents and aldehydes used were purified by distillation before use. Other chemicals like CatBH (1.0 M solution in THF) were purchased from Aldrich or Janssen and used as received. Sia_2BH,[18] Chx_2BH,[17] (-)-Ipc_2BH,[19] Icr_2BH (from (+)-2-carene),[20] and 9-BBN[17] were prepared and purified according to the literature procedure.

(*Z*)-4-Phenyl-3-buten-2-one. 4-Phenyl-3-butyn-2-one (2.9 g, 20 mmol) was selectively reduced to (*Z*)-4-phenyl-3-buten-2-one (2.5 g, 86%) using Lindlar catalyst (0.2 g) in pentane (25 mL) at room temperature and atmospheric pressure:[21] IR 1685 cm^{-1}; ^{1}H NMR 7.3–7.5 (m, 5 H), 6.91 (d, J = 12.7 Hz, 1 H), 6.19 (d, J = 12.7 Hz, 1 H), 2.17 (s, 3 H).

(*E*)-3-Methyl-3-penten-2-one. Prepared in 55% yield (1.1 g) from (*E*)-2-methyl-2-butenoic acid (2.0 g, 20 mmol) and 1.4 M methyllithium (55 mL, 77 mmol) in THF (50 mL) at 0 °C;[22] after 2 h at 0 °C the reaction mixture was quenched with Me_3SiCl (10 mL) followed by water (20 mL). The pH of the aqueous phase was adjusted to neutrality with $NaHCO_3$, and after extraction with ether the collected organic phases were dried over Na_2SO_4 and the title ketone was purified by spinning-band distillation: bp 125 °C; IR 1670 cm^{-1}; ^{1}H NMR 6.74 (qq, J = 1.3 and 6.9 Hz, 1 H, H4), 2.28 (s, 3 H, H1), 1.85 (dq, J = 1.1 and 6.9 Hz, 3 H, H5), 1.75 (pseudoquintet, J ~ 1.1 Hz, 3 H).

(*E*)-4-Phenyl-3-propenethioic Acid, *S*-Phenyl Ester. Prepared in 82% yield (9.8 g) from cinnamoyl chloride (8.3 g, 50

(18) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses with Boranes*; Wiley-Interscience: New York, 1975.
(19) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.
(20) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.
(21) Fieneman, H.; Koebrick, G. *Chem. Ber.* **1974**, *107*, 2801.
(22) Rubottom, G. M.; Kim, C. w. *J. Org. Chem.* **1983**, *48*, 1550.

mmol) and benzenethiolate supported on Amberlyst A-26 anion exchanger (65 g) in THF (70 mL) according to Manescalchi:[23] IR 1660 cm^{-1}; ^1H NMR 7.70 (d, J = 15.9 Hz, 1 H, H3), 7.4 (m, 10 H, ArH), 6.82 (d, J = 15.9 Hz, 1 H, H2).

Hydroboration of 4-Hexen-3-one with Dicyclohexylborane (Table I, Entry 2): Typical Procedure. 4-Hexen-3-one (0.10 g, 1 mmol) dissolved in $CDCl_3$ (3 mL) is added to a solution of freshly prepared dicyclohexylborane (0.21 g, 1.2 mmol) in the same solvent (1.5 mL) cooled at 0 °C. A yellow or orange color immediately appears, and then the reaction is allowed to warm to 20 °C. To quench the reaction, water (3 mL) is added, and then the hydroboration mixture is vigorously stirred at room temperature for 0.5 h, ether is added, and the products are detected by GC analysis.

Reductive Condensation of β-Ionone with Benzaldehyde (Table III, Entry 6): Synthesis of *syn*-4-Hydroxy-3-[(2,6,6-trimethyl-1-cyclohexen-1-yl)methyl]-4-phenyl-2-butanone. Typical Procedure. β-Ionone (1.92 g, 10 mmol) dissolved in THF (10 mL) is added to a slurry or solution of the freshly prepared diisopinocampheylborane (2.87 g, 10 mmol) in the same solvent (10 mL) cooled at 0 °C. The reaction is stirred at 20 °C for 2 h, and then the reaction flask is cooled at −30 °C. Benzaldehyde (1.06 g, 10 mmol) is added over 2 min, the reaction mixture is stirred at −30 °C for 16 h, and the reaction progress is controlled by TLC analysis. Water (30 mL) is added, and the reaction mixture is vigorously stirred for 30 min. After extraction with ether (3 × 30 mL), the ketol (oil, 2.29 g, 77%) is purified by flash chromatography using cyclohexane–ether (9:1). Once the unreacted aldehyde has been eluted, the ether content is gradually increased to 20%. In the case of Ipc_2B enolates, two chromatographic runs are often required in order to get analytically pure ketols. We found that an oxidative workup is not necessary in order to free the ketol and that a major amount of boron oxidation products is present when the reaction is quenched with pH 7 buffered H_2O_2, so making the chromatographic purification more difficult. Furthermore, attempts to complex the boron-derived products with ethanolamine did not make simpler the purification of ketols, and traces of anti isomers were observed: $[\alpha]^{20}_D$ −57.7 (*c* 1.0, $CHCl_3$); IR 3460 (br), 1690, 1200, 1170, 750, 695 cm^{-1}; ^1H NMR 7.30 (m, 5 H, ArH), 4.97 (d, J = 4.6 Hz, 1 H, H4), 3.55 (s, 1 H, OH), 3.15 (ddd, J = 4.0, 4.6, and 11.3 Hz, 1 H, H3), 2.6 (dd, J = 11.3 and 14.5 Hz, 1 H, $COCHCH_2$), 2.33 (dd, J = 4.0 and 14.5 Hz, 1 H, $COCHCH_2$), 2.05 (s, 3 H, H1), 1.90 (m, 2 H), 1.55 (m, 2 H), 1.48 (s, 3 H), 1.42 (m, 2 H), 0.92 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR 19.0 (C), 20.5 (CH_3), 25.3 (CH_2), 28.0 (CH_3), 29.1 (CH_3), 32.8 (CH_2), 33.3 (CH_3), 34.9 (CH_2), 40.1 (=CCH_2CH), 57.5 (C3), 73.9 (C4), 126.4, 127.6, 128.4, 130.6 (C), 134.3 (C), 141.7 (C), 216.6 (C2); MS *m/e* (relative intensity) 43 (100), 239 (92), 79 (60), 77 (59), 121 (71), 193 (53), 91 (48), 161 (43), 282 (13), 300 (10, M^+). Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.88; H, 9.56.

***syn*-4-(Phenylhydroxymethyl)-3-hexanone (Table III, entry 3)**: oil; 1.32 g, 65%; $[\alpha]^{20}_D$ 19.4 (*c* 1.15, $CHCl_3$); IR 3440 (br), 1700, 1450, 1020, 920, 865, 760, 700 cm^{-1}; ^1H NMR 7.35 (m, 5 H, ArH), 4.87 (dd, J = 2.2 and 6.0 Hz, 1 H, PhC*H*OH), 2.84 (ddd, J = 4.2, 6.0, and 9.6 Hz, 1 H, H4), 2.75 (d, J = 2.2 Hz, 1 H, OH), 2.33 (dq, J = 7.2 and 18.3 Hz, 1 H, H2), 2.17 (dq, J = 7.2 and 18.3 Hz, 1 H, H2), 1.75 (m, 2 H, H5), 0.9 (t, J = 7.2 Hz, 3 H, H1), 0.85 (t, J = 7.2 Hz, 3 H, H6); ^{13}C NMR 6.8 (C6), 11.9 (C1), 20.3 (C5), 38.2 (C2), 60.2 (C4), 74.1 (CHOH), 126.3, 127.8, 128.5, 142.3, 216.2 (C3); MS *m/e* (relative intensity) 100 (100), 85 (73), 71 (63), 177 (47), 57 (44), 77 (41), 79 (38), 107 (34), 206 (11, M^+), 188 (10). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.8. Found: C, 75.57; H, 8.9.

***syn*-4-Ethyl-5-hydroxy-3-decanone (Table III, entry 5)**: oil; 1.07 g, 54%; $[\alpha]^{20}_D$ 15.4 (*c* 1.07, $CHCl_3$); IR 3440, 1700, 1455, 1375, 1140, 1105, 1020, 855 cm^{-1}; ^1H NMR 3.75 (dt, J = 4.1 and 8.3 Hz, 1 H, H5), 2.52 (m, 3 H, H2 + H4), 2.42 (s, 1 H, OH), 1.69 (m, 2 H, CH_3CH_2), 1.45 (m, 2 H, H6), 1.29 (m, 6 H, H7 + H8 + H9), 1.05 (t, J = 7.0 Hz, 3 H, H1), 0.90 (2t, 6 H, CH_3CH_2 + H10); ^{13}C NMR 7.3 (CH_3CH_2), 12.4 (C1), 14.0 (C10), 19.7 (CH_2CH_3), 22.7 (CH_2), 25.8 (CH_2), 31.7 (CH_2), 34.5 (CH_2), 37.8 (C2), 58.0 (C4), 71.6 (C5), 216.9 (C3); MS *m/e* (relative intensity) 100 (100), 57 (79), 71 (71), 85 (58), 55 (38), 83 (35), 171 (32), 43 (27), 41 (27), 153 (20), 182 (M^+ − 18, 18), 125 (10), 129 (9), 200 (M^+). Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.76; H, 12.32.

***syn*-4-Hydroxy-3-[(2,6,6-trimethyl-1-cyclohexen-1-yl)methyl]-2-pentanone (Table III, entry 8)**: oil; 1.41 g, 60%; $[\alpha]^{20}_D$ −55.0 (*c* 0.7, $CHCl_3$); IR 3420 (br), 1695, 1155, 1110, 945, 915, 860 cm^{-1}; ^1H NMR 4.00 (quintet, J = 4.5 Hz, 1 H, H4), 3.18 (br s, 1 H, OH), 2.83 (dt, J = 4.5 and 10.8 Hz, H3), 2.48 (dd, J = 10.8 and 14.5 Hz, 1 H, =CCH_2CH), 2.34 (dd, J = 4.5 and 14.5 Hz, 1 H, =CCH_2CH), 2.11 (s, 3 H, H1), 1.90 (m, 2 H), 1.55 (m, 2 H), 1.52 (s, 3 H), 1.40 (m, 2 H), 1.16 (d, J = 4.5 Hz, 3 H, H5), 1.03 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR 19.0 (C), 20.0 (CH_3), 20.6 (CH_3), 25.6 (CH_2), 28.2 (CH_3), 29.2 (CH_3), 32.8 (CH_2), 33.3 (CH_3), 34.9 (CH_2), 40.0 (=CCH_2CH), 56.9 (C3), 68.2 (C4), 130.4 (C), 134.5 (C), 216.4 (C2); MS *m/e* (relative intensity) 122 (100), 43 (90), 161 (47), 95 (41), 81 (37), 69 (37), 136 (34), 176 (32), 105 (32), 194 (18), 205 (11), 195 (11), 220 (M^+ − H_2O, 9), 238 (M^+, 6). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58, H, 10.99. Found: C, 75.90, H, 10.86.

***syn*-5,5-Dimethyl-4-hydroxy-3-[(2,6,6-trimethyl-1-cyclohexen-1-yl)methyl]-2-hexanone (Table III, entry 9)**: oil; 0.83 g, 30%; flash chromatography using CH_2Cl_2 as eluent two runs; $[\alpha]^{20}_D$ 12.05 (*c* 1.1, $CHCl_3$); IR 3460 (br), 1710, 1370, 1355, 1160, 1080, 1020, 945 cm^{-1}; ^1H NMR 4.63 (d, J = 9.4 Hz, 1 H, OH), 3.26 (dd, J = 9.4 and 1.2 Hz, H4), 3.07 (m, 1 H, H3), 2.65 (dd, J = 8.4 and 14.0 Hz, 1 H, =CCH_2CH), 2.37 (dd, J = 6.6 and 14.0 Hz, 1 H, =CCH_2CH), 2.21 (s, 3 H, H1), 1.96 (m, 2 H), 1.60 (m + s, 5 H), 1.44 (m, 2 H), 1.07 (s, 3 H), 0.97 (s, 3 H), 0.85 (s, 9 H, *t*-Bu); ^{13}C NMR 19.0 (C), 20.7 (CH_3), 26.7 (CH_3 *t*-Bu), 28.1 (CH_3), 29.1 (CH_3), 31.7 (CH_2), 32.8 (CH_2), 33.4 (CH_3), 34.9 (CH_2), 36.0 (CH_2), 40.1 (=CCH_2CH), 48.4 (C3), 83.2 (C4), 131.4 (C), 133.9 (C), 218.9 (C2); MS *m/e* (relative intensity) 137 (100), 87 (95), 43 (90), 95 (83), 176 (66), 123 (50), 143 (43), 81 (41), 57 (41), 121 (33), 69 (33), 85 (26), 223 (M^+ − C_4H_9, 14), 280 (M^+, 2), 262 (M^+ − 18, 2). Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.5. Found: C, 77.12, H, 11.47.

***syn*-4-Hydroxy-4-phenyl-3-(phenylmethyl)-2-butanone (Table III, entry 10)**: oil, 2.27 g, 90%; $[\alpha]^{20}_D$ −38.8 (*c* 1.0, $CHCl_3$); IR 3410 (br), 1700, 1600, 1490, 1450, 1365, 1160, 1045, 920, 765, 745, 730, 700 cm^{-1}; ^1H NMR 7.47–7.05 (m, 10 H, ArH), 4.95 (d, J = 5.8 Hz, 1 H, H4), 3.22 (ddd, J = 4.05, 5.8, and 10.9 Hz, 1 H3), 3.00 (m, 3 H, CH_2Ph + OH), 1.62 (s, 3 H, H1); ^{13}C NMR 32.5 (C1), 33.5 ($PhCH_2$), 61.5 (C3), 73.9 (C4), 126.4, 126.5, 128.0, 128.7, 129.0, 139.6, 141.9, 214.0 (C2); MS *m/e* (relative intensity) 148 (100), 105 (100), 43 (96), 91 (80), 77 (68), 92 (63), 70 (52), 106 (50), 163 (22), 236 (4, M^+ − H_2O). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.45; H, 6.95.

***syn*-1,3-Diphenyl-3-hydroxy-2-(phenylmethyl)-1-propanone (Table III, entry 11)**: solid: 2.51 g, 80%; mp 88–89 °C (hexane); $[\alpha]^{20}_D$ −17.0 (*c* 1.04, $CHCl_3$); IR (KBr) 3460 (very br), 1665, 750, 735, 690, 685 cm^{-1}; ^1H NMR 7.6–6.9 (m, 15 H, ArH), 5.13 (dd, J = 2.0 and 4.2 Hz, 1 H, H3), 4.04 (ddd, J = 3.7, 4.2, 11.0 Hz, 1 H, H2), 3.27 (d, J = 2.0 Hz, 1 H, OH), 3.20 (dd, J = 11.0 and 13.5 Hz, 1 H, CH_2Ph), 3.05 (dd, J = 3.7 and 13.5 Hz, 1 H, CH_2Ph); ^{13}C NMR 33.2 ($PhCH_2$), 55.4 (C2), 73.9 (C3), 126.2, 126.3, 127.7, 128.4, 128.5, 129.1, 133.2, 137.5, 139.5, 141.7, 205.3 (C1); MS *m/e* (relative intensity) 77 (100), 105 (91), 210 (71), 106 (36), 51 (15), 91 (12), 211 (12), 78 (8), 225 (1, M^+ − C_7H_7). Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.52; H, 6.37. Found: C, 83.67, H, 6.53.

***syn*-4-Methyl-3-(phenylhydroxymethyl)-2-pentanone (Scheme IV)**: oil, 0.41 g, 20%; IR 3400 (br), 1700, 1600, 1440, 1380, 1365, 1040, 750, 700 cm^{-1}; ^1H NMR 7.25 (m, 5 H, ArH), 4.88 (d, J = 8.25, 1 H, C*H*OH),[24] 2.93 (dd, J = 4.7 and 8.25 Hz, 1 H, H3), 2.42 (s, 1 H, OH), 2.24 (d septet, J = 4.7 and 6.9 Hz, 1 H, H4), 1.78 (s, 3 H, H1), 0.98 (t, J = 6.9 Hz, 6 H); ^{13}C NMR 18.2 (CH_3), 21.8 (CH_3), 27.3 (C4), 33.7 (C1), 64.5 (C3), 73.3 (*C*HOH), 126.7, 128.0, 128.6, 142.9, 212.3 (C2); MS *m/e* (relative intensity) 85 (100), 43 (82), 73 (67), 70 (50), 100 ($C_3H_7CH_2COCH_3$, 37), 163 (M^+ − C_3H_7, 30), 107 (30), 105 (25), 106 (18), 205 (M^+ − 1, 3). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.8. Found: C, 75.62, H, 8.64.

***syn*-3-(Phenylhydroxymethyl)-3-methyl-5-pentanone (Scheme V)**. A mixture (1.66 g) of the title compound and the anti stereoisomer in a 2:1 ratio was obtained by flash chroma-

(23) Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L.; Panunzio, M. *Gazz. Chim. Ital.* **1983**, *113*, 523.

(24) The abnormally high value for a syn ketol of the $J_{a,b}$ coupling constant is due to the bulkiness of the isopropyl group in α-position, which destabilizes the H-bonded cyclic conformation and favors a conformation where H_a and H_b are in antiperiplanar arrangement: see ref 2a, pp 115–117.

tography and was found to be 80% pure by ^{1}H NMR analysis. Two analytically pure samples of syn and anti ketols were obtained by preparative TLC using cyclohexane–ether (8:2): oil; IR 3400 (br), 2920, 1700, 1690, 1450, 1350, 1040, 1000, 920 cm^{-1}; ^{1}H NMR 7.3 (m, 5 H, Ar), 4.89 (d, J = 2.3 Hz, 1 H, C*H*OH), 2.90 (d, J = 2.3 Hz, 1 H, OH), 2.07 (s, 3 H, H1), 1.98 (dq, J = 7.5 and 15 Hz, 1 H, H4), 1.48 (dq, J = 7.5 and 15 Hz, 1 H, H4), 1.06 (s, 3 H, C*H*$_3$CO), 0.88 (t, J = 7.5 Hz, 3 H, H5); upon irradiation of the multiplet at 4.89 ppm a positive NOE effect is observed for signals at 2.07 (1.4%) and 1.06 (1.2%), and this is in agreement with a syn relative configuration if we assume that the title ketol adopts a H-bonded cyclic conformation; ^{13}C NMR 9.0 (*C*H$_3$), 17.9 (*C*H$_3$), 27.0 (C4), 28.1 (*C*H$_3$), 56.0 (C3), 78.5 (*C*HOH), 127.8, 127.9, 128.0, 129.2, 130.0, 140.0, 215.9 (C2); MS m/e (relative intensity) 100 (100), 85 (93), 43 (47), 51 (45), 77 (41), 107 (PhCHOH, 26), 79 (26), 105 (20), 106 (PhCHO, 17), 205 (M$^+$ - 1, 1). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.8. Found: C, 75.71; H, 8.84.

***anti*-3-(Phenylhydroxymethyl)-3-methyl-5-pentanone (Scheme V)**: oil; IR 3400 (br), 2920, 1700, 1690, 1450, 1350, 1040, 1000, 920 cm^{-1}; ^{1}NMR 7.3 (m, 5 H, Ar), 4.97 (d, J = 3.8 Hz, 1 H, C*H*OH), 2.85 (d, J = 3.8 Hz, 1 H, OH), 2.10 (s, 3 H, H1), 1.75 (dq, J = 7.5 and 15 Hz, 1 H, H4), 1.26 (dq, J = 7.5 and 15 Hz, 1 H, H4), 1.05 (s, 3 H, C*H*$_3$CO), 0.80 (t, J = 7.5 Hz, 3 H, H5); upon irradiation of the multiplet at 4.97 ppm a positive NOE effect is observed for signals at 2.10 (1.1%), 1.75 (2.5%), and 1.26 (0.8%), and this is in agreement with an anti relative configuration if we assume that the title ketol adopts a H-bonded cyclic conformation: ^{13}C NMR 8.3 (*C*H$_3$), 15.0 (*C*H$_3$), 27.5 (*C*H$_3$), 29.4 (C4), 56.2 (C3), 78.2 (*C*HOH), 127.8, 127.9, 128.0, 129.2, 130.0, 140.0, 215.9 (C2); MS m/e (relative intensity) 100 (100), 85 (93), 43 (47), 51 (45), 77 (41), 107 (PhCHOH, 26), 79 (26), 105 (20), 106 (PhCHO, 17), 205 (M$^+$ - 1, 1). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.8. Found: C, 75.63; H, 8.64.

***syn*-2-(Phenylmethyl)-3-hydroxy-3-phenylthiopropanoic acid, *S*-phenyl ester (Scheme VI)**: oil; 0.35 g; IR 3500 (br), 1690, 1600, 1450, 1320, 1050, 920, 740, 690 cm^{-1}; ^{1}NMR 7.45–7.2 (m, 11 H, ArH), 7.13 (m, 2 H, ArH), 7.05 (m, 2 H, ArH), 5.12 (dd, J = 2.4 and 5.2 Hz, 1 H, H3), 3.27 (m, 1 H, H2), 3.09 (q, J = 13.5 Hz, 1 H, C*H*$_2$Ph) 3.06 (dd, J = 13.5 and 20.3 Hz, 1 H, C*H*$_2$Ph), 2.79 (d, J = 2.4 Hz, 1 H, OH); ^{13}C NMR 33.5 (*C*H$_2$Ph), 63.1 (C2), 74.1 (C3), 126.5, 126.6, 128.1, 128.6, 128.7, 129.3, 129.4, 129.7, 134.5, 138.8, 202.2 (C1); MS m/e (relative intensity) 110 (100), 91 (97), 77 (94), 105 (86), 133 (72), 107 (59), 51 (52), 161 (14), 221 (13), 242 (10), 348 (M$^+$, 6), 239 (M$^+$ - SPh, 3). Anal. Calcd for $C_{22}H_{20}O_2S$: C, 75.83; H, 5.79. Found: C, 75.67, H, 5.83.

***anti*-2-(Phenylmethyl)-3-hydroxy-3-phenylthiopropanoic Acid, *S*-Phenyl Ester (Scheme VI).** Flash chromatography afforded a fraction (1.08 g) containing the anti and the syn isomers in the 3:1 ratio. We could not isolate an analytically pure specimen of the anti product as it was always contaminated by the syn isomer; so we report here only its characteristic NMR signals, which clearly identify it: ^{1}H NMR 4.88 (t, J = 6.6 Hz, 1 H, H3), 3.30 (m, 1 H, H2), 3.00 (dd, J = 9.5 and 13.1 Hz, 1 H, C*H*$_2$Ph), 2.99 (d, J = 6.6 Hz, 1 H, OH), 2.80 (dd, J = 5.8 and 13.1 Hz, 1 H, C*H*$_2$Ph); ^{13}C NMR 36.3 (*C*H$_2$Ph), 62.3 (C2), 75.1 (C3), 126.4, 126.5, 126.9, 127.4, 128.3, 128.6, 128.7, 128.8, 129.2, 129.3, 129.4, 129.8, 134.6, 138.1, 142.0, 202.0 (C1).

Acknowledgment. We thank the Italian C.N.R. (Progetto Finalizzato Chimica Fine 2) for financial support.

Synthetic Studies toward Rapamycin: A Solution to a Problem in Chirality Merger through Use of the Ireland Reaction

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Received April 15, 1991

A program directed toward a total synthesis of rapamycin is described. This paper reports the synthesis of enoate **36**, a fragment that would correspond to carbons 28–49 of rapamycin. The two building blocks required to reach **36** were allylic alcohol **5** and acid **6**. The former was obtained in a straightforward way from D-(+)-glucose. The route passed through a 5,6-methylene derivative (see structure **12**) that underwent Ferrier transformation to the hydroxycyclohexanone derivative **13**. The acid **6** was built from aldehyde **15**. An addition reaction of allyltrimethylsilane to **15** and a subsequent addition of crotylboronate **18** to aldehyde **17** were the key steps in the chain extension leading to the acid. The central issue of the synthesis was the merging of two chiral sectors (see A and B) to produce an ensemble in which the achiral spacer element consists of a single methylene carbon, C_{39}. This problem was solved by establishing an ester bond between **5** and **6**. The strategic C_{40}–C_{39} carbon–carbon bond was generated by application of the Ireland ester enolate rearrangement. The extraneous carboxyl group (see structure **28**) was removed by photolysis of the *N*-hydroxyphthalimide ester (see transformation **30** → **31**).

Background of the Problem and Synthetic Planning

Rapamycin (**1**), a metabolite of *Streptomyces hygroscopicus*, was first isolated from an Easter Island soil sample.[1,2] Though significant chemistry and extensive spectral measurements were carried out on rapamycin, elucidation of its structure relied on a crystallographic determination.[3,4] With the assignment of **1** secure, the structure of a related substance, 29-demethoxyrapamycin (**2**), could be established by spectroscopic means.[5] Early interest in these compounds arose from their antibiotic properties. During routine toxological studies, it was found that rapamycin alters the histology of lymphoid tissue.

Subsequent studies have centered around the immunosuppressive properties of **1**, with possible application to autoimmune diseases.[6] The scope of the inquiry broadened considerably following discovery of the extraordi-

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0022-3263/91/1956-5826$02.50/0