rameters were fully optimized by MM2.[22]

Registry No. (*S*)-(*Z*)-**5**, 109960-86-3; (*S*)-(*E*)-**5**, 109960-92-1; (*R*)-(*Z*)-**6**, 109960-87-4; (*S*)-(*E*)-**6**, 109960-93-2; (*S*)-(*Z*)-**7**, 109960-88-5; (*S*)-(*E*)-**7**, 109960-94-3; (±)-(*Z*)-**8**, 109960-89-6; (±)-(*E*)-**8**, 109960-95-4; (*S*)-(*Z*)-**9**, 109960-90-9; (*S*)-(*E*)-**9**, 109960-96-5; (*S*)-(*Z*)-**10**, 109960-91-0; (*S*)-(*E*)-**10**, 109960-97-6; (*S*)-(*Z*)-**11**, 109960-71-6; (*S*)-(*E*)-**11**, 109960-72-7; (*S*)-(*Z*)-**12**, 109960-73-8; (*S*)-(*E*)-**12**, 109960-74-9; (*S*)-(*Z*)-**13**, 109960-75-0; (*S*)-(*E*)-**13**, 109975-47-5; (±)-(*Z*)-**14**, 109975-48-6; (±)-(*E*)-**14**, 109960-76-1; (*S*)-(*Z*)-**15**, 109960-77-2; (*S*)-(*E*)-**15**, 109975-49-7; (*S*)-(*Z*)-**16**, 109960-78-3; (*S*)-(*E*)-**16**, 109960-79-4; **17a**, 109960-80-7; **17a** (ent), 110013-46-2; **17b**, 110013-28-0; **17c**, 110013-29-1; **17d**, 110013-30-4; **18a**, 109960-81-8; **18b**, 110013-31-5; **18c**, 110013-32-6; **18d**, 110013-33-7; **19a**, 109960-82-9; **19b**, 110013-34-8; **19c**, 110013-35-9; **19d**, 110013-36-0; **20a**, 109960-83-0; **20b**, 110013-37-1; **20c**, 110013-38-2; **20d**, 110013-39-3; **21a**, 109960-84-1; **21b**, 110013-40-6; **21c**, 110013-41-7; **21d**, 110013-42-8; **22a**, 109960-85-2; **22b**, 110013-43-9; **22c**, 110013-44-0; **22d**, 110013-45-1; **23**, 109960-98-7; **24**, 109960-99-8.

Diastereofacial Selectivity of Enolates

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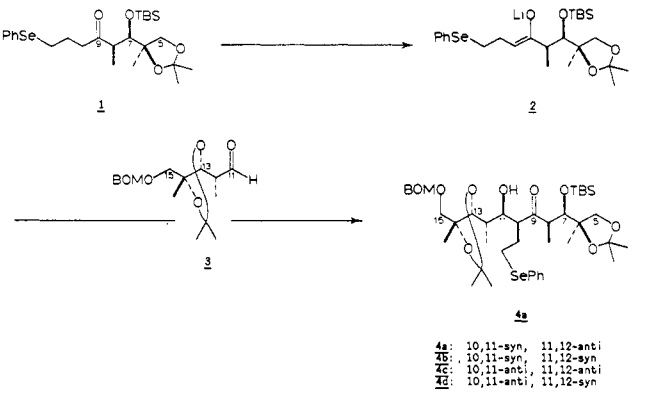
Results from our research in macrolide total synthesis prompted us to investigate ways of altering the diastereofacial selectivity of enolates without making major changes in the enolates' structure. The variation in the diastereofacial selectivity of enolates **7a–g** derived from 3,4-*syn*-3-alkoxy-2,4-dimethylheptan-5-ones (**5a–g**) is presented. The parent enolate **7a** was *si*-facial selective, while protecting the 3-hydroxyl group gave enolates that were *re*-facial selective (**7b–g**). Thus, without changing any chiral centers or backbone functionality, the diastereofacial selectivity of enolates can be varied or reversed. The implications of this finding to natural products synthesis are discussed.

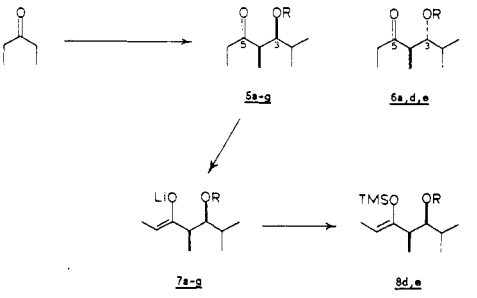
The aldol reaction is of great utility for the total synthesis of complex natural products such as macrolides and ionophores.[2-4] Several investigators have employed aldols for coupling large fragments late in their total syntheses, taking advantage of the reaction's supreme reliability for forming carbon–carbon bonds. Unfortunately, high stereoselectivity from such aldol couplings cannot be relied on. Despite some stunningly good results[5] and a growing understanding of aldol reactions, most aldol reactions used to couple large fragments have resulted in moderate to poor stereoselectivities. Given the potential power of the aldol reaction, it is unfortunate that stereochemical issues limit its utility.

During our study of the total synthesis of streptovaricin A,[6] we investigated the aldol reaction **1** and **3** (Scheme I).[7]

Scheme I



Scheme II



Reaction of ketone **1** with lithium hexamethyldisilazide gave (*Z*)-O-enolate **2** in >20:1 selectivity as judged by enolate-trapping experiments.[11] Reaction of **2** with al-

(1) Current address: Medicinal Chemistry Department, Pfizer Central Research, Groton, CT 06340.

(2) (a) Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic: New York, 1984; p 127. (b) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. (c) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(3) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley-Insterscience: New York, 1982; p 1 and references cited therein. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23 and references cited therein.

(4) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, and references cited therein.

(5) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

(6) McCarthy, P. A. *Tetrahedron Lett.* **1982**, *23*, 4199.

(7) For explanation of syn,anti nomenclature, see ref 2b.

(8) Designation of an enolate's diastereomeric face is made by using a variation of the *re,si* system: Hanson, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 2731. All designations ae made with regard to the oxygen-bearing carbon of the enolate moiety. The priority order is oxygen, the sp^3 carbon, and then the sp^2 carbon. Such designations refer to the same absolute face of all enolates regardless of enolate geometry or substitution.

(9) (a) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

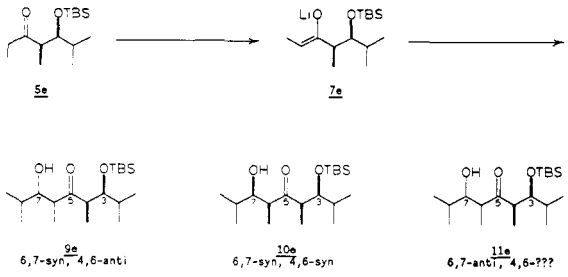
(10) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(11) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

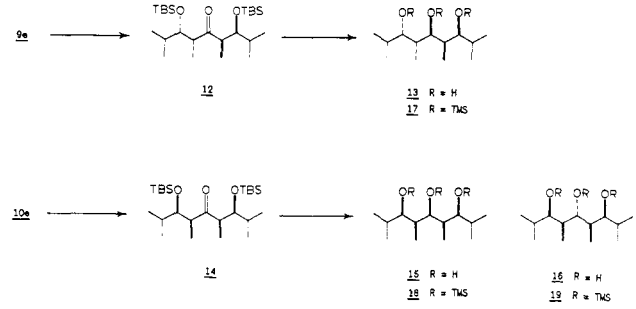
(12) (a) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

0022-3263/87/1952-4681$01.50/0

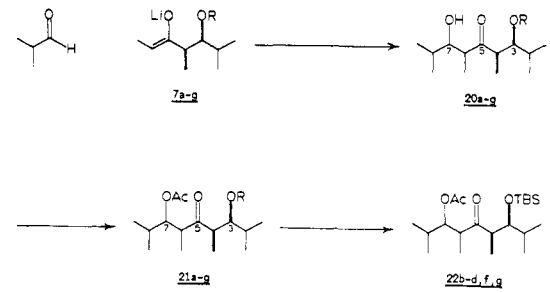
Scheme III



Scheme IV



Scheme V



dehyde **3** provided the aldol products in 74% yield. Unfortunately, formation of all four diastereomeric products was observed (normalized ratio of 1.0:2.6:1.5 for **4a**, **4b**, and **4c** plus **4d**). Since **4a** possessed the stereochemistry required for streptovaricin A, this result was clearly unsatisfactory and we sought to improve the stereoselectivity.

Selectivity of enolate generation and the diastereofacial selectivity of the two reactants are the major factors determining the overall stereoselectivity of the aldol reaction.[3,4] Since we already knew that our enolate generation was highly selective for the desired enolate, we turned to the diastereofacial selectivities of enolate **2** and aldehyde **3**. Reactions of aldehyde **3** with achiral enolates indicated that the diastereoselectivity of aldehyde **3** favored formation of the desired 11,12-anti products. These data led us to suspect that the diastereofacial selectivity of **2** disfavored formation of the desired product; this is, **2** was *re*-facial selective while we needed it to be *si*-facial selective.[8] Furthermore, earlier work suggested that it should be possible to significantly increase the diastereofacial selectivity of aldehyde **3**.[9] For these reasons, we concluded that reversing the enolate's diastereofacial selectivity was the key to improving the overall stereoselectivity of the streptovaricin A aldol reaction.

This conclusion left us with a dilemma. We wanted to improve the overall stereoselectivity of this reaction, but we did not want to make drastic modifications of the enolate, because its basic structure contained the functionality and chirality required for our target molecule. On the other hand, we could easily manipulate the protecting group arrangement of ketone **1**, and it seemed likely that the C_7-hydroxyl group would play a particularly important role in determining the enolate's diastereofacial selectivity. Since we could find no definitive literature reports to support or refute this hypothesis, we chose to study the variation of the diastereofacial selectivity of 3,4-*syn*-3-alkoxy-2,4-dimethylheptan-5-ones (**5a–g**) as a function of its alcohol protecting group.

Ketone **5** was synthesized as shown in Scheme II. This material has been synthesized earlier by using boron enolate chemistry,[10] but since authentic samples of the 3,4-anti diastereomer **6a** were also desired, it was considered more convenient to perform a lithium-mediated aldol. Thus, treatment of 3-pentanone with lithium tetramethyldiphenyldisilazide selectivity produced the (*Z*)-O-enolate.[9a] Addition of isobutyraldehyde gave a mixture of 3,4-syn (**5a**) and 3,4-anti (**6a**) products, which could be separated chromatographically.

The 3-hydroxyl group of **5a** was protected with a variety of groups by known procedures. By use of the same procedures, **6d** and **6e** were synthesized, and these were used to determine the diastereomeric purity of **5d** and **5e** by capillary GLC. The diastereomeric purity of the other ketones was examined without authentic samples of **6**, but in all cases, the ketones **5b–g** were greater than 96% pure. (*Z*)-O-Enolates **7a–g** were selectively generated from ketones **5a–g** with lithium hexamethyldisilazide. The purity of these enolates was established in two cases by enolate-trapping experiments.[11] Both **8d** and **8e** contained less than 1% of the (*E*)-O-enolates.

Generation of (*Z*)-O-enolate **7e** under the aforementioned conditions, followed by addition of isobutyraldehyde, gave a mixture of three aldol products (Scheme III). After chromatographic separation, proton NMR studies of each compound provided the coupling constants between the protons on carbons 6 and 7 ($J_{6,7}$: **9e**, 2.2 Hz; **10e**, 1.7 Hz; **11e**, 6.7 Hz). On the basis of such coupling constants,[4,11] products **9e** and **10e** were assigned 6,7-syn stereochemistry, while **11e** was assigned 6,7-anti stereochemistry. Additionally, both **12** and **14** (see Scheme IV) had symmetrical proton NMR spectra, which further confirms the 6,7-syn assignment.

With the two 6,7-syn products identified, all that remained was to distinguish between their 4,6-stereochemistries. This could be accomplished by using the symmetry that had been designed into these molecules (Scheme IV). Initial attempts to reduce **9e** directly were not clean, so the 6-hydroxyl group was protected by using *tert*-butyldimethylsilyl triflate followed by lithium aluminum hydride reduction and desilylation in the workup to give **13**. When the same procedure was carried out with **10e**, a 94:6 mixture of **15** and **16** was observed. The fact that **9e** gave only one triol while **10e** gave two triols allowed us to assign the stereochemistries shown. However, with such a small amount of the minor triol **16** observed, we felt additional proof of stereochemistry was necessary. The stereochemistries were confirmed by careful examination of the proton and carbon NMR spectra of **13** and **15** as well as their respective tris(trimethylsilyl) ethers **17** and **18**. The proton NMR spectra of **15** and **18** were completely symmetrical,

(13) (a) Neeman, M.; Caserio, M. J.; Roberts, J. D.; Johnson, W. S. *Tetrahedron* **1959**, *6*, 36. (b) Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3. (c) Jonczyk, A.; Wlostowska, J. *Synth. Commun.* **1978**, *8*, 569. (d) Shapiro, R. H. *Org. React. (N.Y.)* **1976**, *23*, 405.

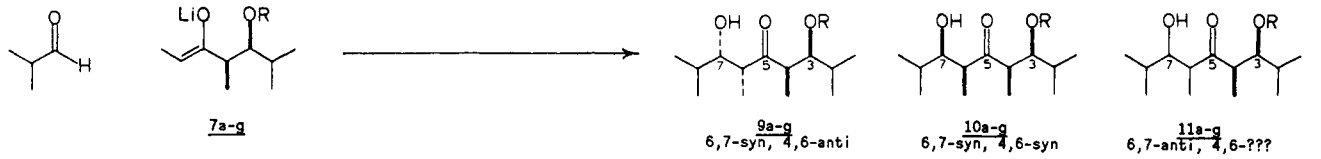
(14) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(15) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(16) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

(17) Purity estimated to be greater than 95% based on TLC and NMR spectral analysis.

Table I[a]



enolate	R	normalized ratios, 9:10:11	DS	KD	yield, %
a	H	1.0:2.1:0.8	2.1	4.0	75
b	Bn	1.1:1.0	1.1		79
c	MEM	1.4:1.0:0.1	1.4	24.0	73
d	BOM	2.0:1.0:0.2	2.0	15.0	81
e	TBS	4.5:1.0:0.4	4.5	13.8	85
f	TMS	6.0:1.0:0.7	6.0	10.0	66
g	TES	6.4:1.0:0.8	6.4	9.3	74

[a] Key: DS = diastereofacial selectivity of enolate (ratio of major 6,7-syn product to minor 6,7-syn product); KD = kinetic diastereoselectivity of enolate (ratio of 6,7-syn products to 6,7-anti products); Bn = benzyl; MEM = (methoxyethoxy)methyl; BOM = (benzyloxy)methyl; TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; TES = triethylsilyl.

while the spectra of **13** and **17** were clearly unsymmetrical. Furthermore, in two different deuteriated solvents, the carbon NMR spectrum of **15** showed 7 lines while that of **13** showed 13 lines. The carbon NMR spectrum of **18** showed 8 lines (all the carbons on the trimethylsilyl groups had the same chemical shift), while the spectrum of **17** showed 16 lines. All of this data allowed us to confidently assign the 4,6-stereochemistry of **9e** and **10e**.

With the stereochemistry of the products determined, other protecting groups were investigated (Scheme V).[18,19] For example, **7c** was allowed to react with isobutyraldehyde to give **20c**, a mixture of three diastereomeric aldol products. This entire mixture was acetylated to give **21c**, which was examined by GLC to get an initial ratio of products. **21c** was then deprotected at C_3 and silylated to give **22c**. By GLC comparison with authentic samples, **22c** was shown to be a 1.4:1.0:0.1 mixture of the acetates of **9e**, **10e**, and **11e**. By use of a similar procedure, enolates **7b,d–g** were also examined. The products derived from enolate **7a** were correlated to 3,7-diacetoxy ketones derived from **21d**.

By use of this procedure, the diastereofacial selectivities of six protected enolates and the parent enolate were determined (Table I). The enolates have been arranged from *si*-facial selective (**7a**) to *re*-facial selective (**7b–7g**). Interestingly, in the case of enolates with protecting groups, the kinetic diastereoselectivity (ratio of 6,7-syn products to 6,7-anti products) drops as the diastereofacial selectivity (ratio of 4,6-anti to 4,6-syn) rises. Enolate **7a** is an exception to this trend; however, **7a** is a dianion that would not be expected to act similarly to the monoanion enolates. It should also be noted that enolate **7e** is *re*-facial selective. This enolate is the closest analogy to the streptovaricin A enolate (**2**), which, using deductive reasoning, we had concluded was *re*-facial selective. The fact that **7e** is *re*-facial selective supports our conclusion.

From the results, it appears that the *si*-facial selectivity of these enolates increases as the β-oxygen becomes a better donating group. However, without more elaborate investigation, we believe one cannot provide a transition-state drawing to explain these results. Be that as it may, the experimental facts carry an important message: an enolate's diastereofacial selectivity can be varied or reversed without changing any chiral centers or backbone functionality. Simple protecting group alterations are enough to vary or reverse the enolate's diastereofacial selectivity.

To appreciate the implications of this finding, we must return to our discussion of aldol couplings in natural product syntheses. Often times, aldol couplings give poor stereochemical results, but the chiral centers and backbone functionality of the enolate and aldehyde are dictated by the target molecule. Changing these would greatly reduce the efficiency of the synthesis. The challenge is to improve stereoselectivity of the aldol coupling without major modification of the reactants.

The results presented in this paper provide an avenue for solving this problem. Since the diastereofacial selectivity of **7** can be changed to favor either *re*-facial or *si*-facial attack, with judicious choice of protecting group, **7** should react with a chiral aldeyde to selectively provide either 6,7-syn, 4,6-anti or 6,7-syn, 4,6-syn products. And given the principle of double asymmetric induction,[4,12] even if the individual diastereofacial selectivities are modest, the overall stereoselectivity can be high, provided that the diastereofacial selectivities are matched. Thus, it should be possible to couple **7** with any chiral aldehyde and get aldol products with high stereoselectivity.

If the variations observed in the diastereofacial selectivity of **7** are representative of what can be expected from protecting group changes, then these results may have widespread implications for optimizing stereoselectivities of aldol couplings in natural product syntheses. The application of these results to the streptovaricin A synthesis will be reported when complete.

Experimental Section

All air- and moisture-sensitive reactions were performed under nitrogen or argon in flasks dried by heating under high vacuum. All reagents were purified and dried before use by normal procedures. THF and ether were distilled from LAH immediately prior to use. Methylene chloride and toluene were refluxed over calcium hydride for several hours, distilled, and stored under argon over 4-Å molecular sieves. Proton NMR spectra were recorded on Bruker WM 250 or 270-MHz FT-NMR. Carbon NMR were recorded on Bruker WM 270 (67.9-MHz) FT-NMR. IR spectra were recorded in solution cells on a Perkin-Elmer 283B infrared spectrophotometer. Mass spectra were recorded on a Varian Matt 44 or a Finnigan MAT 8200. Elemental analyses were performed by Robertson Laboratories of Florham Park, NJ. All GLC work

(18) Structures **20**, **21**, and **22** all represent mixtures of diastereomers. For instance, **20c** is a 1.4:1.0:0.1 mixture of **9c**, **10c**, and **11c**. Although all lots of **22** consist of **9e**, **10e**, and **11e**, the ratios of these diastereomers vary from one lot to another. The lots are referred to in this manner because this is how they were actually dealt with in the laboratory.

(19) This derivatization procedure described here was performed in order to assign the stereochemistry of the diastereomers obtained. As shown in Scheme V, each mixture was acetylated and the individual protecting group was replaced with a *tert*-butyldimethylsilyl group. This allowed for identification of diastereomers through GLC doping experiments using authentic samples of the acetates derived from **9e**, **10e**, and **11e**.

used a Hewlett-Packard capillary GLC.

3-Hydroxy-2,4-dimethylheptan-5-one (5a, 6a). A solution of *n*-BuLi in hexane (37.1 mL, 3.08 M, 0.114 mol) was added to a 0 °C solution of tetramethyldiphenyldisilazane (34.5 mL, 0.119 mol) in dry THF (200 mL). The reaction was stirred at 0 °C for 20 min and then was cooled to −78 °C. 3-Pentanone (8.96 g, 0.104 mol) was added dropwise via syringe. After the resultant mixture was stirred at −78 °C for 1 h, isobutyraldehyde (11.25 g, 0.156 mol) was added dropwise via syringe. After the mixture was stirred for 5 min, pH 6.8 phosphate buffer (200 mL, 0.200 mol) was poured into the reaction flask. The mixture was allowed to warm to room temperature and was then extracted three times with ether. The combined extracts were dried, filtered, cooled to −78 °C (to avoid foaming during concentration), and concentrated to give approximately 60 mL of a mixture of base and aldol products that could not be separated by distillation. The mixture was stored at 0 °C and purified by flash chromatography (1:10–1:1, ether/hexane gradient) portionwise as needed. An overall yield of 75% is estimated based on the amount of product obtained by purification of one lot. **5a**: ^{1}H NMR ($CDCl_3$, D_2O) δ 0.82 (d, 6.73 Hz, 3 H), 0.98 (d, 6.67 Hz, 3 H), 1.03 (t, 7.29 Hz, 3 H), 1.63 (m, 1 H), 2.51 (complex, 2 H), 2.71 (dq, 2.82, 7.26 Hz, 1 H), 3.48 (dd, 2.82, 8.47 Hz, 1 H); IR ($CHCl_3$) 3500 (m), 1692 (s) cm^{-1}. **6a**: ^{1}H NMR ($CDCl_3$, D_2O) δ 0.88 (d, 6.76 Hz, 3 H), 0.92 (d, 6.86 Hz, 3 H), 1.02 (t, 7.31 Hz, 3 H), 1.08 (d, 7.15 Hz, 3 H), 1.69 (m, 1 H), 2.50 (complex, 2 H), 2.74 (dq, 6.48, 7.15 Hz, 3 H), 3.40 (dd, 5.09, 6.48 Hz, 3 H); IR ($CHCl_3$) 3620 (m), 3490 (m), 1702 (s) cm^{-1}. These data compare favorably with that reported earlier for these compounds.[10]

3,4-*syn*-3-(Benzyloxy)-2,4-dimethyl-5-heptanone (5b). By use of published procedures,[13] **5a** was benzylated with use of fluoroboric acid and phenyldiazomethane to give 0.027 g (7% yield) of **5b**. Capillary GLC analysis showed this material to be >97% diastereomerically pure:[17] ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 6.76 Hz, 3 H), 0.95 (d, 6.75 Hz, 3 H), 1.03 (t, 7.28 Hz, 3 H), 1.16 (d, 6.85 Hz, 3 H), 1.73 (m, 1 H), 2.50 (q, 7.28 Hz, 2 H), 2.78 (dq, 6.23, 6.85 Hz, 1 H), 3.50 (dd, 5.67, 6.23 Hz, 1 H), 4.50 (s, 2 H), 7.24–7.32 (m, 2 H); IR ($CHCl_3$) 1700 (s) cm^{-1}.

3,4-*syn*-3-[(Methoxyethoxy)methoxy]-2,4-dimethyl-5-heptanone (5c). (Methoxyethoxy)methyl chloride (0.165 g, 1.33 mmol) was added to a room temperature solution of **5a** (0.070 g, 0.442 mmol) and diisopropylethylamine (0.228 g, 1.77 mmol) in methylene chloride (1.5 mL). The resulting mixture was stirred at room temperature for 15 h and then quenched with saturated aqueous sodium bicarbonate. This mixture was extracted three times with ether, and the combined organic extracts were dried, filtered, and concentrated to give crude **5c**. PTLC (1:3, ether/hexane) provides 0.082 g (75% yield) of pure **5c**. Capillary GLC analysis showed this material to be >97% diastereomerically pure: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6.71 Hz, 3 H), 0.91 (d, 6.89 Hz, 3 H), 1.01 (t, 7.18 Hz, 3 H), 1.07 (d, 6.87 Hz, 3 H), 1.70 (m, 1 H), 2.50 (m, 2 H), 2.72 (dq, 5.47, 6.87 Hz, 1 H), 3.35 (s, 1 H), 3.49 (m, 2 H), 3.59 (dd, 5.47, 5.55 Hz, 1 H), 3.64 (m, 2 H), 4.66 (d, 7.04 Hz, 1 H), 4.68 (d, 7.04 Hz, 1 H); IR ($CHCl_3$) 1703 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64. Found: C, 63.60; H, 10.45.

3,4-*syn*-3-[(Benzyloxy)methoxy]-2,4-dimethyl-5-heptanone (5d). By use of a procedure similar to that described for **5c**, **5a** was protected with (benzyloxy)methyl chloride and diisopropylethylamine to give 0.092 g (71% yield) of **5d**. Capillary GLC analysis showed this material to be >97% diastereomerically pure: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 6.72 Hz, 3 H), 0.94 (d, 6.75 Hz, 3 H), 1.00 (t, 7.27 Hz, 3 H), 1.12 (d, 6.96 Hz, 3 H), 1.73 (m, 1 H), 2.50 (m, 2 H), 2.76 (dq, 5.53, 6.96 Hz, 1 H), 3.66 (dd, 5.53, 5.58 Hz, 1 H), 4.57 (s, 2 H), 4.71 (d, 7.34 Hz, 1 H), 4.73 (d, 7.34 Hz, 1 H), 7.24–7.32 (m, 5 H); IR ($CHCl_3$) 1710 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.11; H, 9.66.

3,4-*anti*-3-[(Benzyloxy)methoxy]-2,4-dimethyl-5-heptanone (6d). By use of a procedure similar to that described for **5c**, **6a** was protected with (benzyloxy)methyl chloride and diisopropylethylamine to give 0.087 g (64% yield) of **6d**. Capillary GLC analysis showed this material to be >99% diastereomerically pure:[17] ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6.81 Hz, 3 H), 0.97 (d, 6.69 Hz, 3 H), 0.99 (d, 6.77 Hz, 3 H), 1.00 (t, 7.29 Hz, 3 H), 1.84 (m, 1 H), 2.51 (q, 7.29 Hz, 2 H), 2.86 (dq, 6.71, 8.33 Hz, 1 H), 3.60 (dd, 3.25, 8.33 Hz, 1 H), 4.50 (d, 11.93 Hz, 1 H), 4.58 (d, 11.93 Hz, 1 H), 4.63 (d, 6.63 Hz, 1 H), 4.68 (d, 6.63 Hz, 1 H), 7.25–7.32 (m, 5 H); IR ($CHCl_3$) 1710 (s) cm^{-1}.

3,4-*syn*-3-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethyl-5-heptanone (5e). By use of published procedures,[14] **5a** was silylated with *tert*-butyldimethylsilyl triflate and 2,6-lutidine to give 0.443 g (63% yield) of **5e**. Capillary GLC analysis showed this material to be >99% diastereomerically pure: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 3 H), 0.04 (s, 3 H), 0.81 (d, 6.84 Hz, 3 H), 0.87 (d, 6.35 Hz, 3 H), 0.88 (s, 9 H), 1.01 (t, 7.13 Hz, 3 H), 1.05 (d, 7.33 Hz, 3 H), 1.58 (m, 1 H), 2.48 (complex, 2 H), 2.67 (dq, 6.02, 7.33 Hz, 1 H), 3.75 (dd, 4.12, 6.02 Hz, 1 H); IR ($CHCl_3$) 1705 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 65.84; H, 11.70.

3,4-*anti*-3-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethyl-5-heptanone (6e). By use of published procedures,[14] **6a** was silylated with *tert*-butyldimethylsilyl triflate and 2,6-lutidine to give 0.103 g (81% yield) of **6e**. Capillary GLC analysis showed this material to be >98% diastereomerically pure:[17] ^{1}H NMR ($CDCl_3$) δ −0.09 (s, 3 H), 0.02 (s, 3 H, 0.84 (s, 9 H), 0.87 (d, 7.27 Hz, 6 H), 0.94 (d, 7.17 Hz, 3 H), 0.99 (t, 7.15 Hz, 3 H), 1.71 (d of septets, 3.07, 7.27 Hz, 1 H), 2.49 (complex, 2 H), 2.72 (dq, 7.17, 7.72 Hz, 1 H), 3.76 (dd, 3.07, 7.72 Hz, 1 H); IR ($CHCl_3$) 1712 (s) cm^{-1}.

3,4-*syn*-3-[(Trimethylsilyl)oxy]-2,4-dimethyl-5-heptanone (5f). By use of published procedures,[14] **5a** was silylated with trimethylsilyl triflate and 2,6-lutidine to give 0.151 g (79% yield) of **5f**. Capillary GLC analysis showed this material to be >98% diastereomerically pure:[17] ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9 H), 0.82 (d, 6.11 Hz, 3 H), 0.85 (d, 6.42 Hz, 3 H), 1.01 (t, 7.31 Hz, 3 H), 1.05 (d, 7.39 Hz, 3 H), 1.54 (m, 1 H), 2.46 (q, 7.31 Hz, 3 H), 2.66 (dq, 6.38, 7.39 Hz, 1 H), 3.71 (dd, 4.54, 6.38 Hz, 1 H); IR ($CHCl_3$) 1700 (s) cm^{-1}.

3,4-*syn*-3-[(Triethylsilyl)oxy]-2,4-dimethyl-5-heptanone (5g). By use of published procedures,[14] **5a** was silylated with triethylsilyl triflate and 2,6-lutidine to give 0.143 g (88% yield) of **5g**. Capillary GLC analysis showed this material to be >98% diastereomerically pure:[17] ^{1}H NMR ($CDCl_3$) δ 0.59 (q, 7.95 Hz, 6 H), 0.82 (d, 6.81 Hz, 3 H), 0.87 (d, 6.78 Hz, 3 H), 0.94 (t, 7.95 Hz, 9 H), 1.01 (t, 7.32 Hz, 3 H), 1.07 (d, 7.23 Hz, s H), 1.58 (m, 1 H), 2.46 (dq, 1.75, 7.32 Hz, 2 H), 2.66 (dq, 6.42, 7.23 Hz, 1 H), 3.76 (dd, 4.24, 6.42 Hz, 1 H); IR ($CHCl_3$) 1700 (s) cm^{-1}.

3,4-*syn*-3-[(Benzyloxy)methoxy]-5-[(trimethylsilyl)oxy]-2,4-dimethyl-5-heptene (8d). A solution of *n*-BuLi in hexane (0.352 mL, 2.53 M, 0.890 mmol) was added to a 0 °C solution of hexamethyldisilazane (0.305 g, 1.068 mmol) in dry THF (1.5 mL). The reaction was stirred at 0 °C for 20 min and then was cooled to −78 °C. A 78 °C solution of **5d** (0.194 g, 0.712 mmol, dried by azeotropic removal of water with toluenee in THF (1.0 mL and 1.0-mL and 1.0-mL rinse) was added dropwise via cannula. After the mixture was stirred at −78 °C for 1 h, trimethylchlorosilane (0.155 g, 1.424 mmol) was added dropwise via syringe, and the mixture was allowed to warm to room temperature. After being stirred at room temperature for 1 h, the mixture was quenched with saturated aqueous sodium bicarbonate (10 mL) and extracted three times with ether. The combined extracts were dried, filtered, and concentrated to give 0.523 g of crude product mixed with some hexamethyldisilazane residue. Capillary GLC analysis showed only one silylenol ether, which was assigned (*Z*)-O geometry based on NMR data: ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9 H), 0.91 (d, 6.65 Hz, 3 H), 0.98 (d, 6.93 Hz, 3 H), 1.00 (d, 6.93 Hz, 3 H), 1.46 (d, 6.71 Hz, 3 H), 1.83 (m, 1 H), 2.22 (m, 1 H), 3.44 (dd, 4.83, 6.56 Hz, 1 H), 4.54 (d, 11.97 Hz, 1 H), 4.58 (q, 6.71 Hz, 1 H), 4.69 (d, 5.31 Hz, 1 H), 4.71 (d, 5.31 Hz, 1 H), 4.72 (d, 11.97 Hz, 1 H), 7.25–7.32 (m, 5 H).

3,4-*syn*-3-[(*tert*-Butyldimethylsilyl)oxy]-5-[(trimethylsilyl)oxy]-2,4-dimethyl-5-heptene (8e). By use of a procedure identical with the one described for **8d**, **5e** was treated with lithium hexamethyldisilazide and trimethylchlorosilane to give crude **8e** mixed with some hexamethyldisilazane residue (quantitative yield). Capillary GLC analysis showed only one silylenol ether, which was assigned (*Z*)-O geometry on the basis of NMR data: ^{1}H NMR ($CDCl_3$) δ −0.03 (s, 3 H), 0.01 (s, 3 H), 0.17 (s, 9 H), 0.85 (d, 7.09 Hz, 6 H), 0.87 (s, 9 H), 0.95 (d, 7.21 Hz, 3 H), 1.46 (d, 6.63 Hz, 3 H), 1.76 (m, 1 H), 2.14 (dq, 5.18, 7.21 Hz, 1 H), 3.51 (dd, 5.02, 5.18 Hz, 1 H), 4.47 (q, 6.63 Hz, 1 H).

General Procedure for Aldol Coupling: 3-[(Triethylsilyl)oxy]-7-hydroxy-2,4,6,8-tetramethyl-5-nonanone (20g).[19]

A solution of *n*-BuLi in hexane (0.187 mL, 2.91 M, 0.545 mmol) was added to a 0 °C solution of tetramethyldiphenyldisilazane (0.188 mL, 0.645 mmol) in dry THF (1.0 mL). The reaction was stirred at 0 °C for 20 min and then was cooled to −78 °C. A −78 °C solution of **5g** (0.119 g, 0.436 mmol, dried by azeotropic removal of water with toluene) in THF (1.0 mL and 1.0-mL rinse) was added dropwise via cannula. After the mixture was stirred at −78 °C for 1 h, isobutyraldehyde (0.063 g, 0.872 mmol) was added dropwise via syringe. After being stirred for 5 min, the mixture was quenched with pH 7.0 phosphate buffer (8.0 mL), 0.50 M). The mixture was allowed to warm to room temperature and extracted three times with ether. The combined extracts were dried, filtered, and concentrated to give 0.329 g of **20g**, a mixture of three diastereomeric aldol products.[18] Aldol products **20a–f** were also synthesized by this procedure.

Acetic anhydride (1.0 mL) was added to **20g** in pyridine (2.0 mL). The resulting mixture was stirred at room temperature for 12 h, and then the volatiles were removed under high vacuum to give crude **21g**. The ratio of diastereomeric acetates was determined by capillary GLC. Crude **21g** was then purified by flash chromatography (1:10–1:2, ether/hexane gradient) to give 0.124 g (73% yield) of **21g**, a mixture of three diastereomeric acetylated aldol products.[18] Major diastereomer: ^{1}H NMR of ($CDCl_3$) δ 0.58 (q, 7.96 Hz, 6 H), 0.83 (d, 6.77 Hz, 3 H), 0.86 (d, 6.23 Hz, 3 H), 0.91 (t, 7.29 Hz, 9 H), 0.92 (d, 7.42 Hz, 3 H), 0.95 (d, 8.10 Hz, 3 H), 1.01 (d, 6.81 Hz, 3 H), 1.02 (d, 6.77 Hz, 3 H), 1.57 (m, 1 H), 1.83 (m, 1 H), 2.00 (s, 3 H), 2.96 (dq, 5.20, 6.81 Hz, 1 H), 3.01 (dq, 4.29, 6.77 Hz, 1 H), 3.61 (dd, 4.40, 5.20 Hz, 1 H), 4.99 (dd, 4.29, 7.77 Hz, 1 H); ($CHCl_3$) 1727 (s), 1710 (s) IR cm^{-1}. Anal. Calcd for $C_{21}H_{42}O_4Si$: C, 65.23; H, 10.95. Found: C, 64.95; H, 11.09. This material was reanalyzed by capillary GLC to show that no change had occurred in the diastereomeric ratio. Acetylated aldol products **21a–f** was also synthesized and analyzed by this procedure.

General Correlation Procedure: 3-[(*tert*-Butyldimethylsilyl)oxy]-7-acetoxy-2,4,6,8-tetramethyl-5-nonanone (22g).[19] By use of a published procedure,[15] **21g** (0.056 g, 0.163 mmol) was desilylated with acetic acid, water, and THF. The resulting product was silylated with *tert*-butyldimethylsilyl triflate and 2,6-lutidine according to a published procedure to give 0.058 g (92% yield) of **22g**. By GLC comparison with authentic samples, **22g** was shown to be a 6.4:1.0:0.8 mixture of the acetates of **9e**, **10e**, and **11e** (vide infra).[18] Major acetate: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.85 (d, 6.85 Hz, 3 H), 0.86 (d, 6.91 Hz, 3 H), 0.87 (s, 9 H), 0.89 (d, 6.85 Hz, 3 H), 0.92 (d, 6.91 Hz, 3 H), 1.01 (d, 6.95 Hz, 3 H), 1.02 (d, 6.96 Hz, 3 H), 1.60 (m, 1 H), 1.82 (m, 1 H), 2.00 (s, 3 H), 2.94 (m, 1 H), 2.96 (m, 1 H), 3.61 (dd, 4.20, 4.48 Hz, 1 H), 4.98 (dd, 4.36, 7.51 Hz, 1 H); IR ($CHCl_3$ 1730 (s), 1715 (s) cm^{-1}. Anal. Calcd for $C_{21}H_{41}O_4Si$: C, 65.23; H, 10.95. Found: C, 65.49; H, 10.94.

Correlation products **22b–d,f** were also synthesized and analyzed by this route, except the deprotection procedure varied. **21b** and **21d** were deprotected by hydrogenation using palladium on carbon, followed by silylation to give **22b** and **22d**, respectively. **21c** was deprotected with zinc bromide,[16] followed by silylation to give **22c**. **21f** was deprotected with pyridinium fluoride in pyridine and THF, followed by silylation to give **22f**.

This same correlation procedure was not feasible with **21a**, thus another route was used. A second lot of **21d** was deprotected by hydrogenation and acetylated, giving a mixture to which **21a** could be correlated.

3-[(*tert*-Butyldimethylsilyl)oxy]-7-hydroxy-2,4,6,8-tetramethyl-5-nonanones (9e, 10e, 11e). Another lot of **20e** was purified by repeated flash chromatography (1:10–1:1, ether/hexane gradients) to provide pure samples of **9e**, **10e**, and **11e**.[17] **9e**: ^{1}H NMR ($CDCl_3$, D20) δ 0.02 (s, 3 H), 0.05 (s, 3 H), 0.83 (d, 6.73 Hz, 3 H), 0.84 (d, 6.73 Hz, 3 H), 0.88 (s, 9 H), 0.89 (d, 6.81 Hz, 3 H), 1.00 (d, 6.59 Hz, 3 H), 1.05 (d, 7.24 Hz, 3 H), 1.09 (d, 7.26 Hz, 3 H), 1.60 (m, 1 H), 1.63 (m, 1 H), 2.85 (dq, 6.86, 7.24 Hz, 1 H), 2.8m (dq, 2.19, 7.26 Hz, 1 H), 3.41 (dd, 2.19, 8.75 Hz, 1 H), 3.79 (dd, 2.98, 6.86 Hz, 1 H); IR ($CHCl_3$) 3500 (m), 1690 (s) cm^{-1}. **10e**: ^{1}H NMR ($CDCl_3$, D_{20}) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.81 (d, 6.58 Hz, 3 H), 0.83 (d, 6.56 Hz, 3 H), 0.88 (d, 6.67 Hz, 3 H), 0.88 (s, 9 H), 1.01 (d, 6.59 Hz, 3 H), 1.06 (d, 6.19 Hz, 3 H), 1.09 (d, 6.32 Hz, 3 H), 1.60 (m, 1 H), 1.62 (m, 1 H), 2.89 (dq, 1.72 Hz, 1 H), 2.91 (dq, 3.84 Hz, 1 H), 3.44 (dd, 1.72, 9.15 Hz, 1 H), 3.65 (dd, 3.84, 5.78 Hz, 1 H); IR ($CHCl_3$ 3520 (m), 1688 (s) cm^{-1}. **11e**: ^{1}H NMR ($CDCl_3$, D_{20}) δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.83 (d, 6.75 Hz, 3 H), 0.88 (s, 9 H), 0.89 (d, 6.71 Hz, 3 H), 0.90 (d, 6.80 Hz, 3 H), 0.94 (d, 6.84 Hz, 3 H), 1.08 (d, 7.23 Hz, 6 H), 1.58 (m, 1 H), 1.69 (m, 1 H), 2.84 (dq, 6.72, 7.23 Hz, 1 H), 2.87 (dq, 7.00, 7.23 Hz, 1 H), 3.39 (dd, 4.98, 6.72 Hz, 1 H), 3.80 (dd, 2.87, 7.00 Hz, 1 H); IR ($CHCl_3$) 3625 (m), 3505 (m), 1695 (s) cm^{-1}.

3,4-*syn*-4,6-*anti*-6,7-*syn*- and 3,4-*syn*-4,6-*syn*-6,7-*syn*-3,7-Bis[(*tert*-butyldimethylsilyl)oxy]-2,4,6,8-tetramethyl-5-nonanone (12, 14). By use of a published procedure,[14] **9e** and **10e** were silylated with *tert*-butyldimethylsilyl triflate to give **12** and **14** in 100% and 87% yields, respectively.[17] **12**: ^{1}H NMR ($CDCl_3$) 0.01 (s, 6 H), 0.04 (s, 6 H), 0.84 (d, 7.03 Hz, 6 H), 0.88 (s, 18 H), 0.90 (d, 6.96 Hz, 6 H), 1.05 (d, 7.18 Hz, 6 H), 1.57 (m, 2 H), 2.82 (dq, 5.27, 7.18 Hz, 2 H), 3.76 (dd, 3.45, 5.27 Hz, 2 H); IR ($CHCl_3$) 1698 (s) cm^{-1}. **14**: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.05 (s, 6 H), 0.83 (d, 6.76 Hz, 6 H), 0.88 (d, 6.72 Hz, 6 H), 0.88 (s, 18 H), 1.09 (d, 7.15 Hz, 6 H), 1.55 (m, 2 H), 2.78 (dq, 5.64, 7.15 Hz, 2 H), 3.79 (dd, 3.42, 5.64 Hz, 3 H); IR ($CHCl_3$) 1698 (s) cm^{-1}.

3,4-*syn*-4,6-*syn*-6,7-*syn*-3,5,7-Trihydroxy-2,4,6,8-tetramethyl-5-nonanone (13). A solution of lithium aluminum hybride in ether (1.5 mL, 1.0 M) was added dropwise via syringe to a room temperature solution of **12** (0.032 g, 0.075 mmol) in THF (2.0 mL). The mixture is stirred at room temperature for 16 h and then cautiously quenched with wet THF (2 mL). After the mixture was stirred at room temperature for 10 min, powdered anhydrous sodium sulfate (2 g) was added, and the mixture was stirred for an additional 30 min. Filtration, concentration, and PTLC (3:1, ether/hexane) purification provided 0.011 g (65% yield) **13**:[17] ^{1}H NMR ($CDCl_3$) δ 0.78 (d, 6.87 Hz, 3 H), 0.82 (d, 6.70 Hz, 6 H), 0.87 (d, 708 Hz, 3 H), 0.98 (d, 6.66 Hz, 3 H), 1.01 (d, 6.67 Hz, 3 H), 1.69 (m, 2 H), 1.83 (m, 2 H), 2.93 (br s, 3 H), 3.34 (dd, 1.80, 9.41 Hz, 1 H), 3.50 (dd, 1.87, 9.42 Hz, 1 H), 3.73 (dd, 1.99, 9.86 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 4.51, 9.53, 18.94, 19.00, 19.53, 20.18, 31.07, 31.58, 35.14, 37.30, 76.41, 78.93, 83.46; ^{13}C NMR (C_6D_6) δ 5.39, 10.28, 19.48, 19.71, 20.26, 21.00, 31.84, 32.35, 36.11, 38.31, 76.87, 79.65, 83.89; IR ($CHCl_3$) 3430 (m) cm^{-1}.

3,4-*syn*-4,6-*syn*-6,7-*syn*-3,5,7-Trihydroxy-2,4,6,8-tetramethyl-5-nonanone (15, 16). By use of the same procedure as used to make **13**, **10e** was reduced with lithium aluminum hydride to give a 92% yield of **15** and a 6% yield of **16**.[17] **15**: ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 6.70 Hz, 6 H), 0.91 (d, 7.18 Hz, 6 H), 1.01 (d, 6.51 Hz, 6 H), 1.67 (br s, 3 H), 1.71 (m, 2 H), 1.90 (ddq, 1.76, 6.25, 6.51 Hz, 2 H), 3.55 (dd, 1.76, 9.45 Hz, 2 H), 3.62 (t, 6.25 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.39, 19.07, 19.87, 31.30, 36.01, 77.20, 79.15; ^{13}C NMR (C_6D_6) δ 11.21, 19.67, 20.54, 32.03, 36.99, 77.57, 79.86; IR ($CHCl_3$) 3430 (m) cm^{-1}.

3,4-*syn*-4,6-*anti*-6,7-*syn*-3,5,7-Tris[(trimethylsilyl)oxy]-2,4,6,8-tetramethyl-5-nonanone (17). By use of a literature procedure,[14] **13** was silylated with trimethylsilyl triflate and 2,6-lutidine to give **17**: ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 9 H), 0.10 (s, 9 H), 0.11 (s, 9 H), 0.76 (d, 6.90 Hz, 3 H), 0.78 (d, 6.67 Hz, s H), 0.83 (d, 6.86 Hz, 3 H), 0.84 (d, 6.58 Hz, 3 H), 0.86 (d, 6.36 Hz, 3 H), 0.92 (d, 6.79 Hz, 3 H), 1.67 (m, 3 H), 1.86 (m, 1 H), 3.38 (dd, 2.31, 8.75 Hz, 1 H), 3.51 (dd, 3.53, 5.75 Hz, 1 H), 3.60 (dd, 2.13, 7.52 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 1.10, 1.28, 1.48, 10.80, 11.95, 14.98, 18.17, 20.15, 21.30, 29.54, 32.67, 38.73, 40.64, 75.28, 78.04, 79.33; IR ($CHCl_3$) 2955 (s), 1242 (s), 1020 (s), 825 (s) cm^{-1}. Anal. Calcd for $C_{22}H_{52}O_3Si_3$: C, 58.86; H, 11.68. Found: C, 59.05; H, 11.93.

3,4-*syn*-4,6-*syn*-3,57-Tris[(trimethylsilyl)oxy]-2,4,6,8-tetramethyl-5-nonanone (18). By use of a literature procedure,[14] **15** was silylated with trimethylsilyl triflate and 2,6-lutidine to give **18**:[17] ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 18 H), 0.10 (s, 9 H), 0.83 (d, 6.88 Hz, 12 H), 0.84 (d, 6.82 Hz, 6 H), 1.73 (m, 4 H), 3.55 (dd, 4.25, 6.82 Hz, 2 H), 3.57 (t, 5.80 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 1.13, 12.23, 16.82, 20.43, 31.96, 41.37, 76.75, 78.30.

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5d, 110118-06-4; **5e**, 110118-07-5; **5f**, 110118-08-6; **5g**, 110118-09-7; **6a**, 71699-34-8; **6d**, 110118-10-0; **6e**, 110118-11-1; **7a**, 110142-60-4; **7b**, 110142-61-5; **7c**, 110142-62-6; **7d**, 110142-63-7; **7e**, 110142-64-8; **7f**, 110142-65-9; **7g**, 110142-66-0; **8d**, 110118-12-2; **8e**, 110118-13-3; **9a**, 110118-15-5; **9b**, 110118-16-6; **9c**, 110118-17-7; **9d**, 110118-18-8; **9e**, 110118-19-9; **9f**, 110118-20-2; **9g**, 110118-14-4; **10a**, 110172-21-9; **10b**, 110172-23-1; 10c, 110172-25-3; **10d**, 110172-27-5; **10e**, 110172-29-7; **10f**, 110172-30-0; **10g**, 110172-19-5; **11a**, 110172-22-0; **11b**, 110172-24-2; **11c**, 110172-26-4; **11d**, 110172-28-6; **11e**, 110221-06-2; **11f**, 110172-31-1; **11g**, 110172-20-8; **12**, 110118-26-8; **13**, 110118-27-9; **14**, 110172-41-3; **15**, 110172-42-4; **16**, 110172-43-5; **17**, 110118-28-0; **18**, 110172-44-6; **21a** (isomer 1), 110118-22-4; **21a** (isomer 2), 110172-34-4; **21a** (isomer 3), 110172-35-5; **21b** (isomer 1), 110118-23-5; **21b** (isomer 2), 110172-36-6; **21b** (isomer 3), 110172-37-7; **21c** (isomer 1), 110118-24-6; **21c** (isomer 2), 110172-38-8; **21c** (isomer 3), 110172-39-9; **21d** (isomer 1), 110118-25-7; **21d** (isomer 2), 110172-40-2; **21d** (isomer 3), 110221-00-6; **21e** (isomer 1), 110142-57-9; **21e** (isomer 2), 110221-07-3; **21e** (isomer 3), 110142-58-0; **21f** (isomer 1), 110142-59-1; **21f** (isomer 2), 110221-08-4; **21f** (isomer 3), 110267-52-2; **21g** (isomer 1), 110118-21-3; **21g** (isomer 2), 110172-32-2; **21g** (isomer 3), 110172-33-3; 3-pentanone, 96-22-0; isobutyraldehyde, 78-84-2; (methoxethoxy)methyl chloride, 3970-21-6; (benzyloxy)methyl chloride, 3587-60-8; *tert*-butyldimethylsilyl triflate, 69739-34-0; trimethylsilyl triflate, 27607-77-8; triethylsilyl triflate, 79271-56-0.

Role of Cage Return and Solvent Viscosity in the Temperature-Dependent Kinetics of Benzylic Bromination

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The effect of temperature on both the kinetic isotope effect in the homolytic abstraction of benzylic hydrogen by bromine and the competitive brominations of toluene and a ring-substituted toluene was interpreted as being due not only to the activation parameters involved in abstraction but upon the viscosity dependence of the kinetic results. Internal cage return was shown to be viscosity dependent, and the resultant kinetic isotope effect was corrected to account for cage reversal. The viscosity dependence in the relative rates of competitive bromination of toluene and *p*-chlorotoluene showed an inverse correlation to that obtained with temperature. The nonmonotonic Arrhenius plot previously reported could be explained on the basis of these two opposing effects, as well as the fact that over the range of temperature previously reported the reaction mixtures became nonhomogeneous.

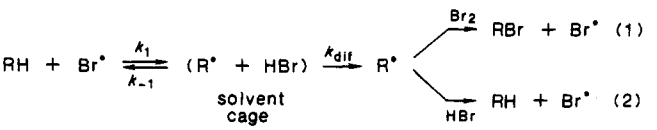
Introduction

A number of years ago we reported that the intermolecular deuterium isotope effect, for the photoinitiated bromination of cyclohexane and perdeuteriocyclohexane, under conditions where the radicals formed do not transfer with the free hydrogen bromide produced (eq 2), was different in the vapor phase and in solution.[1] The difference between the vapor-phase and solution results was shown to result from a cage reversal reaction, between the radical–hydrogen bromide pair, which is competitive with diffusion, see Scheme I.

These results were used to satisfactorily rationalize the reported differences found between the intramolecular deuterium isotope effect reported for the solution[2] and vapor[3] phase photobromination of toluene.

A related phenomena has been recognized for the reaction of radical pairs (*tert*-butyl radicals) in both the vapor phase and in solution. The viscosity of the solvent imposed an anisotropic preference for disproportionation to that of combination, (k_d/k_c), as the viscosity of the solvent increased.[4,5] Prior to these studies the effect of temperature upon the ratio, k_d/k_c, was rationalized as being due to differences in the activation parameters between the two processes.[6] However, the anisotropic phenomena enabled the temperature effect to be explained as a change in the rate ratios, k_d/k_c, as a function of the temperature dependence of the viscosity of the media.[7]

Scheme I



Recently two studies have been reported that involve the temperature-dependent kinetics of benzylic bromination: one measured the temperature dependence of the intermolecular deuterium isotope effect observed for the benzylic bromination of toluene[8] while the other reported the effect of temperature on the relative rates of benzylic bromination for several substituted toluenes.[9] Neither of these studies addressed the question as to whether solvent cage phenomena had an influence on their results.

Deuterium Isotope Effect. The method of determining the temperature dependence of the kinetic isotope effect for the abstraction of a benzylic hydrogen by a bromine atom was an indirect one. The relative rate of hydrogen abstraction from toluene vs. abstraction from

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