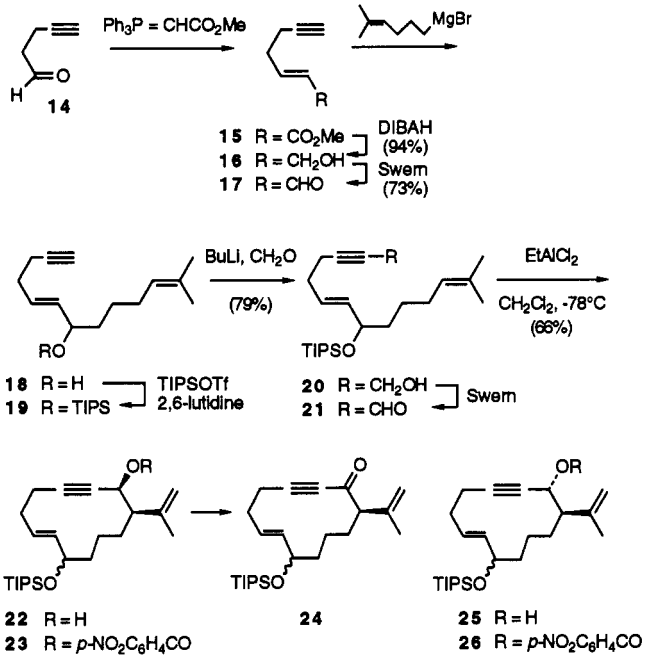
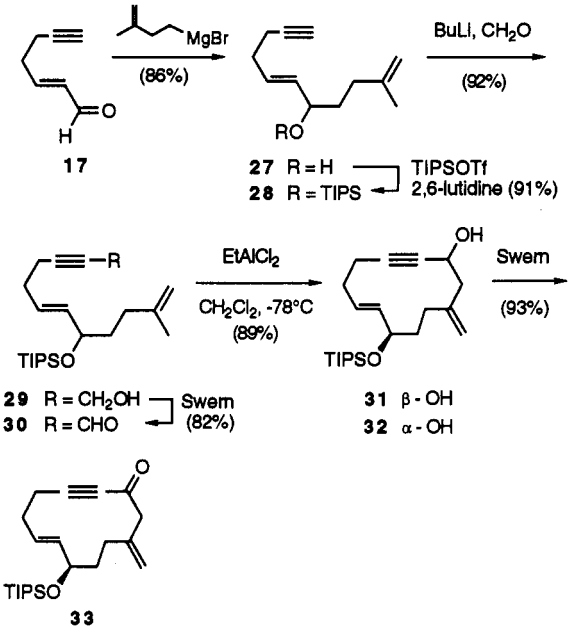
alcohols **22** and **25**. Careful chromatography of the alcohol mixture yielded a pure cis fraction, a mixed cis fraction, and a mixed trans fraction, **25**. The derived *p*-nitrobenzoates **23** and **26** showed coupling for the carbinyl



protons of ca. 4 (cis), 10.1 (major trans), and 8.9 Hz (minor trans). Coupling constants derived from molecular mechanics minimized structures were significantly lower for the diastereomeric cis isomers **22** vs trans isomers **25**.[11] In the absence of chemical correlations, these stereochemical assignments must be regarded as tentative. Interestingly, none of the trans isomers **25** could be detected in the ^1H NMR spectrum of the cyclization product **22**.

The isopropenyl ynal **30** underwent a facile type-II cyclization upon treatment with $EtAlCl_2$ in CH_2Cl_2 at −78 °C affording a 1:1 mixture of diastereomeric alcohols **31** and **32** in 89% yield. Upon oxidation this mixture afforded a single ketone **33** in 93% yield.



The foregoing preliminary results show that ene-type cyclizations can be employed for large as well as normal-size rings. Though less stereoselective than the related allylstannane methodology, the approach employs more accessible olefinic ynal precursors. In some cases stereoselective reductions of the derived ketone can be used to improve unfavorable diastereomeric ratios as illustrated for **7**/**8** → **11**. Extensions to other ring sizes and experiments with chiral Lewis acid catalysts are currently under investigation.

Acknowledgment. Support for this work by the National Institute of General Medical Sciences of the NIH through Research Grant GM 29475 is gratefully acknowledged. Seeds for the ene-type macrocyclization approach to cembranoids were sown by Dr. K. H. Shulte-Elte during discussions following a seminar by J. A. Marshall at Firmenich (Geneva) on May 19, 1991.

Supplementary Material Available: Experimental procedures for all intermediates and selected ^1H and ^{13}C NMR spectra (44 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) The program MacroModel V 3.1x was employed for these calculations. The TIPS grouping was replaced by *t*-Bu to simplify the calculations. Each structure was subjected to a 1000-step Monte Carlo conformational search in the automated set up mode. For each of the four diastereomers multiple conformers (8-20) were found within 4 kJ of the "global" minimum. Hence, the actual coupling constants are most likely average values. MacroModel V 3.1x was obtained from Professor W. Clark Still to whom we are grateful.

The Osmium-Catalyzed Asymmetric Dihydroxylation: A New Ligand Class and a Process Improvement[†,‡]

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Received March 16, 1992

Summary: Two key improvements in the osmium-catalyzed asymmetric dihydroxylation have led to a simple procedure which is applicable to a wide range of olefins.

The catalytic asymmetric dihydroxylation (AD) of olefins (Scheme I)[1] has been improved steadily during the

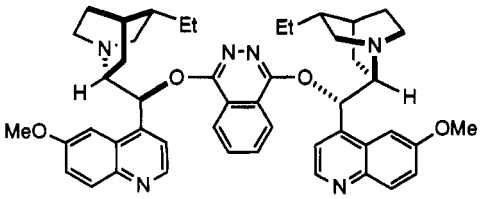
[†] Dedicated to Professor Robert H. Grubbs on the occasion of his 50th birthday.

[‡] Both the phthalazine ligand class and the sulfonamide effect were discovered in the Chemistry Department of the Massachusetts Institute of Technology during our final months there in mid-1991.

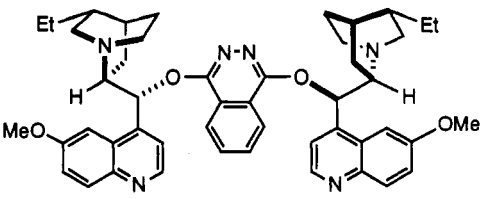
(1) Two comments on conventions from our earlier papers[2] on this subject: (1) ADH has been abbreviated further to AD and (2) the face selection scheme of the earlier reports (i.e., top/bottom attack) won out over the scheme in our last paper,[2g] which entailed bottom/bottom attack and required flipping the olefin (but also note that the steric blocking features of the mnemonic in ref 2g have been added to the present scheme).

0022-3263/92/1957-2768$03.00/0

Chart I

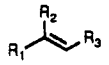
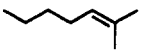
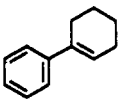
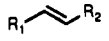
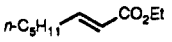
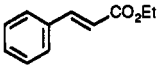
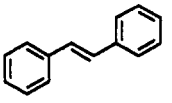
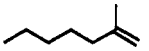
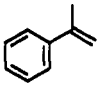
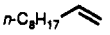
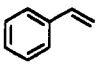
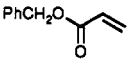
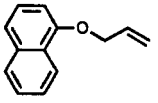


$(DHQD)_2$-PHAL, **1**
Ligand used in AD-mix-β



$(DHQ)_2$-PHAL, **2**
Ligand used in AD-mix-α

Table I. Enantiomeric Excesses (% ee)[a] of the Diols Resulting from Catalytic Asymmetric Dihydroxylation (AD)

			AD-mix-β		AD-mix-α		
class of olefin[b]	entry	olefin[c]	$(DHQD)_2$-PHAL % ee	confign[d]	$(DHQ)_2$-PHAL % ee	confign[d]	$CH_3SO_2NH_2$
	1		98	(*R*)[e]	95	(*S*)[e]	+
	2		99	*R,R*	97	*S,S*	+
	3		97	*R,R*	93	*S,S*	+
	4		99[f]	(2*S*,3*R*)[e]	96	(2*R*,3*S*)[e]	+
	5		97[f,g]	2*S*,3*R*	95[g]	2*R*,3*S*	+
	6		>99.5	*R,R*	>99.5	*S,S*	+
	7		78	*R*	76	*S*	–
	8		94	*R*	93	*S*	–
	9		84	*R*	80	*S*	–
	10		97	*R*	97	*S*	–
	11		77	*S*	70	*R*	–
	12		91	*S*	88	*R*	–

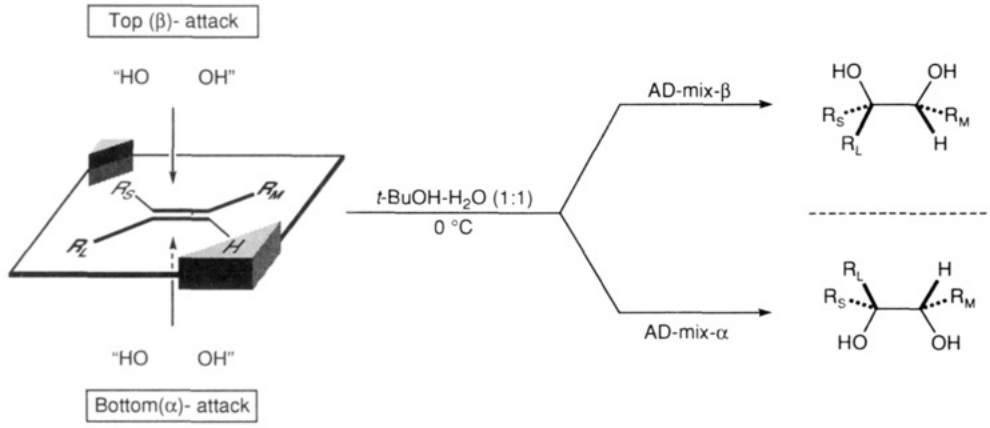
[a] Enantiomeric excesses were determined by HPLC, or ^{19}F NMR analysis of the MTPA esters (see supplementary material). [b] The times of the reactions varied from 6 to 24 h. [c] All olefins are commercially available except entry 12: Rao, A. V. R., Gurjar, M. K., Joshi, S. V. *Tetrahedron: Asymmetry* **1990**, *1*, 697. [d] The absolute configurations of the diols were determined by comparison of their optical rotations with literature values. [e] For entries 1 and 4 the relative configurations are tentatively assigned by comparison with the optical rotations of closely related diols and from the retention times of the bis-MTPA ester (entry 4) on HPLC (see supplementary material). [f] The corresponding methyl ester gave excellent ee and very good yield. [g] These two reactions were performed at room temperature.

past 4 years,[2] but even the most optimistic among us did not anticipate the events of recent months: the two new discoveries are the phthalazine class of ligands[3] (Chart I) and the acceleration of osmate ester hydrolysis in the

(2) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *Ibid.* **1989**, *111*, 1123. (c) Lohray, B. B.; Kalantar, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041. (d) Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Ibid.* **1990**, *31*, 2999. (e) Shibata, T.; Gilheany, D. G.; Blackburn, B. K.; Sharpless, K. B. *Ibid.* **1990**, *31*, 3817. (f) McKee, B. H.; Gilheany, D. G.; Sharpless, K. B. *Org. Synth.* **1991**, *70*, 47. (g) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. (h) Ogino, Y.; Chen, H.; Manoury, E.; Shibata, T.; Beller, M.; Lübben, D.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 5761. (i) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.*, in press.

(3) These ligands were prepared by mixing dihydroquinidine (for ligand 1) or dihydroquinine (for ligand 2) (0.153 mol), 1,4-dichlorophthalazine (Aldrich and see Supplementary Material) (0.078 mol), and potassium carbonate (0.23 mol) in toluene (500 mL). After heating the mixture at reflux for 2 h, potassium hydroxide pellets (0.23 mol) were added and the mixture was refluxed for 12 h with azeotropic removal of water under nitrogen atmosphere (see Supplementary Material for experimental details). We have also found that the quinine and quinidine analogues of ligands 1 and 2 are virtually identical in effectiveness to 1 and 2 in the AD process, despite the fact that the operative ligands are the corresponding tetrols formed by rapid in situ dihydroxylation of the two vinyl groups. Quinine and quinidine are substantially less expensive than their dihydro derivatives.

Scheme I



presence of organic sulfonamides. Taken together these advances have led to one general procedure which is applicable to a wide range of olefinic substrates.

Since this new system is superior to its predecessors in virtually every way,[4] the results in Table I are presented without comparison to the best previous data.[2g] Four of the six olefin substitution classes now have representatives which exceed 90% ee, and entries of >95% ee make up half of Table I. Mirror-image reciprocity between **1** and **2** is closer (e.g., entry 10) than with any of our previous quinidine/quinine-based ligand classes.

Beyond the good to excellent enantiomeric excesses recorded in Table I, the AD has reached a new level of experimental simplicity. An AD-mix formulation[5] of the standard reactants has been developed which simplifies performing the AD on a millimole scale, where only trace amounts of the ligand and the osmium salt are required. These key trace components (0.6% by wt) are blended into the bulk ingredients ferricyanide and carbonate (99.4% by wt) producing a convenient yellow powder. This AD-mix is stable for months when protected from prolonged exposure to moisture. All the examples described in Table I were performed using AD-mix under the *single set of experimental conditions* given below.

A 25-mL round-bottomed flask, equipped with a magnetic stirrer, was charged with 5 mL of *tert*-butyl alcohol, 5 mL of water, and 1.4 g of AD-mix-α or AD-mix-β.[6] Stirring at room temperature produced two clear phases; the lower aqueous phase appears bright yellow. [Methanesulfonamide (95 mg, 1 equiv based on 1 mmol of olefin) was added at this point *only if* the olefin is in the trisubstituted or 1,2-disubstituted classes (i.e., entries 1–6). No $CH_3SO_2NH_2$ should be added for terminal olefins (i.e., entries 7–12).] The mixture was cooled to 0 °C whereupon some of the dissolved salts precipitated. One mmol of olefin was added at once, and the heterogeneous slurry was stirred vigorously at 0 °C for 6–24 h (see Table I) (progress was monitored by TLC or GLC). While the mixture was stirred at 0 °C, solid sodium sulfite (1.5 g) was added and the mixture was allowed to warm to room temperature and stirred for 30–60 min. Ethyl acetate or methylene chloride (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent (3 × 5 mL) (when methanesulfonamide was used, the combined organic layers were washed with 2 N KOH). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated to give the diol and the ligand. This crude product was purified by flash chromatography (silica gel, EtOAc/hexanes; the ligand does not move in this solvent system) to afford the 1,2-diol in 80–98% yield.

In the above procedure the $CH_3SO_2NH_2$ additive was used and is recommended for all nonterminal olefins. The sulfonamide effect is due to an enhanced rate of osmate(VI) ester hydrolysis. Therefore, in those cases (i.e., entries 1–6) where osmate ester hydrolysis is turnover limiting, the presence of $CH_3SO_2NH_2$ leads to shorter reaction times, occasionally as much as 50 times shorter.[7] Due to this sulfonamide effect, most AD reactions can, and should, be run at 0 °C.[8] [Many factors affecting this ligand-accelerated asymmetric transformation are enhanced by operating at lower temperature.[9]] By contrast, all the terminal olefins (e.g., entries 7–12) so far examined actually react slower in the presence of $CH_3SO_2NH_2$.

The amount of chiral ligand needed decreases dramatically with temperature. In the present recipe only 1 mol % (i.e., 2 mM ligand at 0.2 M olefin) of **1** or **2** is used to formulate the AD-mix. This low ligand-loading can be dropped even further without much effect on the % ee. For example, when only $^1/_{100}$ of 1 mol % (20 μM) ligand is used, AD of stilbene still gives 96% ee! At this low level there are now 10000 molecules of stilbene and 20 molecules of OsO_4 for every molecule of chiral ligand,[9] and yet the ligand still manages to provide its services to 9600 molecules of the olefin leaving only 400 molecules for OsO_4 to handle alone—dramatic evidence of the benefits of ligand-accelerated catalysis.[2a]

(4) We find that certain terminal olefins (mono- and 1,1-disubstituted) with branching substituents on the allylic[2i] and homoallylic carbons give better or equivalent ee's using the previously reported phenanthryl ether ligand.[2g] If you wish to know how these or other unpublished results might affect the outcome for a specific olefinic substrate, please FAX us at (619) 554-6406.

(5) Recipe for the preparation of 1 kg of AD-mix-α or AD-mix-β: potassium osmate [$K_2OsO_2(OH)_4$] (0.52 g) and $(DHQ)_2$–PHAL (for AD-mix-α) (5.52 g) or $(DHQD)_2$–PHAL (for AD-mix-β) were ground together to give a fine powder, then added to powdered $K_3Fe(CN)_6$ (700.0 g) and powdered K_2CO_3 (294.0 g), and finally mixed in a blender in a dry box for about 30 min. The resulting mixture should be kept dry and is ready for use. These two AD-mixes are now available from Aldrich.

(6) The 1.4 g of AD-mix-β, necessary for conversion of 1 mmol of the olefin, contains 0.980 g of $K_3Fe(CN)_6$ (3.0 mmol), 0.410 g of K_2CO_3 (3.0 mmol), 0.0078 g of $(DHQD)_2$–PHAL (0.01 mmol), and 0.000 74 g of $K_2OsO_2(OH)_4$ (0.002 mmol). While these AD-mixes are convenient for small-scale reactions (up to 5 mmol), we usually add the individual components separately for larger scale applications.

(7) For example, in the absence of methanesulfonamide, *trans*-5-decene (entry 3) was only 70% converted to the corresponding diol after 3 days at 0 °C, whereas in the presence of methanesulfonamide the diol was obtained in 97% yield (97% ee) after 10 hours at 0 °C.

(8) For olefins which react sluggishly at 0 °C the reaction should be allowed to warm to room temperature. Ethyl cinnamate is such a case and is the only entry in Table I which was run at 25 °C.

(9) Sharpless, K. B. and co-workers. Manuscript in preparation.

The combination of great effectiveness and ready availability should make the new phthalazine cinchona derivatives 1 and 2 the AD's workhorse ligands for some time to come. Nevertheless, terminal olefins are the most common and important members of the olefin family and since most representatives are still below the 90% ee level (Table I, entries 7–12), the search for new ligands continues.

Acknowledgment. Financial support was provided by the National Science Foundation (CHE-8903218) and the National Institutes of Health (GM-28384). W.A. and J.H. thank the Deutsche Forschungsgemeinschaft (DFG) for providing fellowships. We are grateful to Yun Gao of Sepracor Inc., Roy A. Johnson of Upjohn, Edward Grabowski of Merck, and Pui Tong Ho for helpful discussion.

Supplementary Material Available: Experimental procedures and spectral data (^1H and ^{13}C NMR, IR, HRMS, and combustion analyses) for compounds 1 and 2, an improved preparation for 1,4-dichlorophthalazine, the preparation of AD-mix, and analytical data (HPLC, GLC retention times of the diols or their MTPA esters and the optical rotations of the diols) (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Highly Diastereoselective Alkylations of Chiral Amide Enolates: New Routes to Hydroxyethylene Dipeptide Isostere Inhibitors of HIV-1 Protease

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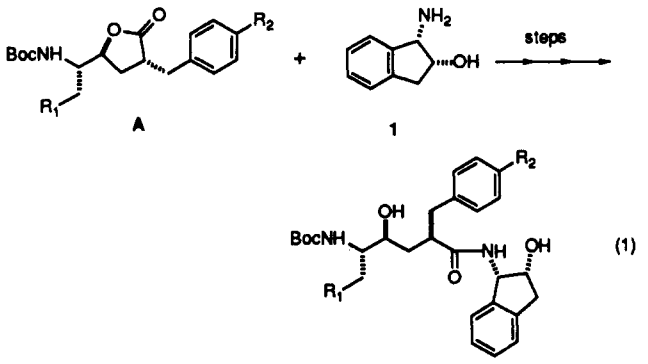
Received February 11, 1992

Summary: The nonchelate enforced chiral amide enolates derived from 4–7 react with alkyl iodide and protected α-amino epoxide electrophiles to produce the HIV protease inhibitors 10 and 16–19 with high diastereoselectivity.

The hydroxyethylene dipeptide isostere (HDI) transition-state mimetics have been found to be potent and selective inhibitors of aspartic acid proteases such as renin.[1] More recently, inhibition of the aspartic acid protease of HIV-1[2] has been recognized as an attractive target for therapeutic intervention in AIDS since inactivation of the protease results in cessation of the posttranslational processing of the viral *gag* and *gag-pol* gene products.

In previous reports from these laboratories, HDIs bearing the cyclic phenylglycine surrogate (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol (1) have been demonstrated to be potent and selective inhibitors of HIV-1 protease.[3] Initial synthetic routes to these compounds (eq 1) proceeded from a "trans"-lactone intermediate[4] A and 1 via the four-step sequence of lactone saponification, hydroxyl group protection, amide bond formation, and hydroxyl deprotection.[5] However, a more concise and practical route was desired. Herein we disclose novel chemistry leading to an efficient, highly diastereoselective coupling of chiral amide and epoxide partners to afford HDIs, as well as a rapid entry into a novel pseudo-C_2-symmetrical inhibitor, each derived from aminoindanol 1. Although many elegant approaches to HDIs have been reported,[6] we



16 R_1 = Ph, R_2 = H

17 R_1 = Ph, R_2 = OCH_2CH_2N⟨O⟩

18 R_1 = Ph, R_2 = OH

19 R_1 = cyclohexyl, R_2 = OCH_2CH_2OH

† Medicinal Chemistry.

(1) *Aspartic Proteinases and Their Inhibitors*; Kostka, V., Ed.; De Gruyter: New York, 1985; p 421–441.

(2) (a) Navia, M. A.; Fitzgerald, P. M. D.; McKeever, B. M.; Leu, C.-T.; Heimbach, J. C.; Herber, W. K.; Sigal, I. S.; Darke, P. L.; Springer, J. P. *Nature* **1989**, *337*, 615–620. (b) Wlodawer, A.; Miller, M.; Jaskolski, M.; Sathyanarayana, B. K.; Baldwin, E.; Weber, I. T.; Selk, L. M.; Clawson, L.; Schneider, J.; Kent, S. B. H. *Science* **1989**, *245*, 616–621. (c) Kohl, N. E.; Emini, E. A.; Schleif, W. A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A. F.; Scolnick, E. M.; Sigal, I. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4686–4690.

(3) Lyle, T. A.; Wiscount, C. M.; Guare, J. P.; Thompson, W. J.; Anderson, P. S.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Dixon, R. A.; Sigal, I. S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 1228–1230.

(4) (a) Prepared from the unsubstituted lactone[4b] in 95% diastereoselectivity via enolization with 2 equiv of LDA followed by alkylation with the corresponding benzylic iodides at −78 °C: Askin, D.; Wallace, M.; Volante, R. P.; Shinkai, I. Unpublished results. (b) Decamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867–1870.

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