tatively, the high selectivity described above. In the transition states T_S and T_R proposed for the reaction of **12a–c** and **13a–c** with an aldehyde, the substituents attached to the chiral center(*) of the enolate reagent are so oriented as to minimize the steric congestion (Chart II). The interactions of cyclohexyl moiety with the (circled) vinylic hydrogen and the ligands attached to boron are avoided as shown in T_S and T_R. Thus, the stereochemistry of the chiral center dictates the approach of the enolate with respect to the aldehyde [approach from the α face of the aldehyde as depicted in T_S, from the β face as shown in T_R] which is translated into the absolute configuration of the final aldol product.

Reaction of **12a–c** or **13a–c** with a chiral aldehyde is of great interest. We have already demonstrated recently that the high diastereoselectivity of a chiral enolate can outweigh many other factors[15] (such as the Cram/anti-Cram selectivity of the aldehyde[16]) which influence the enolate approach to the aldehyde. As a consequence, the stereochemistry at both 2 and 3 positions of compounds **2** and **3**, relative to those existing in (chiral) *R*, can be controlled.[3d] The diastereoselectivity of our new reagents **12** and **13** is far superior to that of our earlier reagents[3d] and exhibits the remarkable stereochemical control in many complex cases as exemplified in the following paper.[5]

Acknowledgment. We thank the National Institutes of Health (AI 15403) and Hoffmann-La Roche for generous financial support. B.I. is a recipient of a Kennedy Memorial Trust Fellowship. High-resolution mass spectra were provided by the facility, supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann), from the Biotechnology Resources Branch, Division of Research Resources.

Supplementary Material Available: A listing of spectral data (4 pages). Ordering information is given on any current masthead page.

(15) Masamune, S. Lecture presented at the Third IUPAC Symposium on Organic Synthesis, held at Madison, WI, June 15–20; *Pure Appl. Chem.*, in press.

(16) For recent reviews, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175–285. (b) Morrison, J. D.; Mosher, H. S. In "Asymmetric Organic Reactions"; American Chemical Society: Washington, DC, 1976.

Total Synthesis of 6-Deoxyerythronolide B

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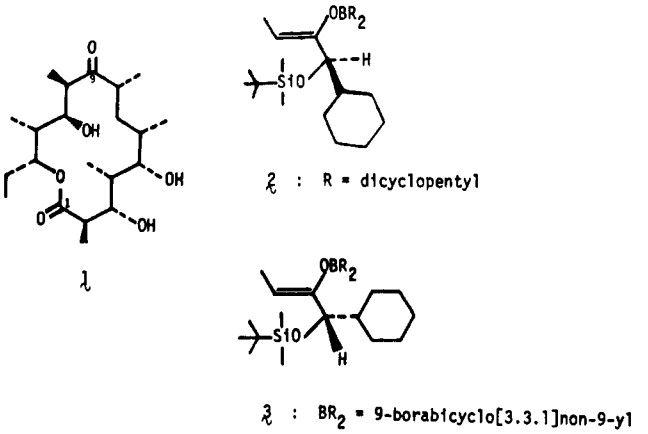
6-Deoxyerythronolide B (**1**), produced by blocked mutants of *Streptomyces erythreus*, is a common biosynthetic precursor leading to all the erythromycins presently known.[1-3] The structure of **1** is rich in chirality: ten asymmetric centers are embedded in the monocyclic, 14-membered lactone system. With the development of new synthetic methodology utilizing the chiral boron enolates **2** and **3** outlined in the preceding paper,[4] the aldol strategy has now been utilized successfully in the synthesis of **1** (Chart I). All of the crucial carbon–carbon bond forming reactions involved in the construction of the carbon framework are exclusively aldol condensations, and more importantly, the *overall* stereoselection of these *four* reactions now reaches 85%. This achievement fulfills an objective originally set for this synthetic project and demonstrates the state of the art in the stereochemical control of this complex reaction. A summary of the synthesis of **1** follows.

Chart I



1 **2** **3** : BR_2 = 9-borabicyclo[3.3.1]non-9-yl

The seco-acid derivative **4** formally derived from **1** is divided into two portions [the left-hand fragment (C_{11}–C_{13}) (**5**) and the right-hand one (C_1–C_{10}) (**6**)] (Scheme I), each of which has been synthesized.

Left-Hand Fragment 5. The enantioselective synthesis (selectivity 100:1, 85% yield) of the corresponding hydroxy acid **7**, using propionaldehyde and the *R*-chiral reagent (**2**), is already described.[4] A sequence of routine operations consisting of methylation (CH_2N_2), triethylsilylation, reduction [$(i\text{-}C_4H_9)_2AlH$], and Collins' oxidation convert **7** into **5**[5] in 75% overall yield.

Right-Hand Fragment 6. The construction of **6** starts with the C_5–C_9 fragment (see **6**). The condensation of (−)-aldehyde **8**[6] with the *S*-chiral reagent (**3**) proceeds smoothly (85% yield, stereoselection 40:1) to provide an aldol product (**9**)[5] which, after successive treatments with hydrogen fluoride and sodium metaperiodate, is converted quantitatively into the Prelog–Djerassi lactonic acid (**10**)[6-8] $[\alpha]_D^{25}$ +47.5° (*c* 1.10, $CHCl_3$) (Scheme II). Thus, this compound **10**, a key intermediate in the syntheses of several natural products, is most readily available in multigram quantities and in optically pure form. Not surprisingly, when (−)-**8** is reacted with the corresponding *R* reagent, compound **9′** becomes the predominant product (stereoselection of 15:1 in favor of **9′**). This aldol product **9′** is converted to **10′** with the structure indicated.[6a] Thus, this set of aldol reactions clearly demonstrates that with both reagents one can indeed create the *syn*-3-

* The authors wish to dedicate this article to Professor George Hermann Büchi on the occasion of his 60th birthday.

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(5) The specific rotations $[\alpha]_D$ (°C, concentration) in $CHCl_3$ of compounds prepared in this work are **4** (24, 0.61) −26.2; **5** (27, 2.50) +49.8; **6** (25, 1.86) −37.0; **7** (25.5, 1.72) +4.1; **8** (25, 0.785) −18.7; **9** (24.5, 2.17) −17.2; **11** (26, 3.62) +27.0 (crude); **12** (24.5, 3.90) +37.3; **13** (26, 1.74) +22.3; **14** (25, 0.41) −33.5; **20** (26, 0.14) −51.0.

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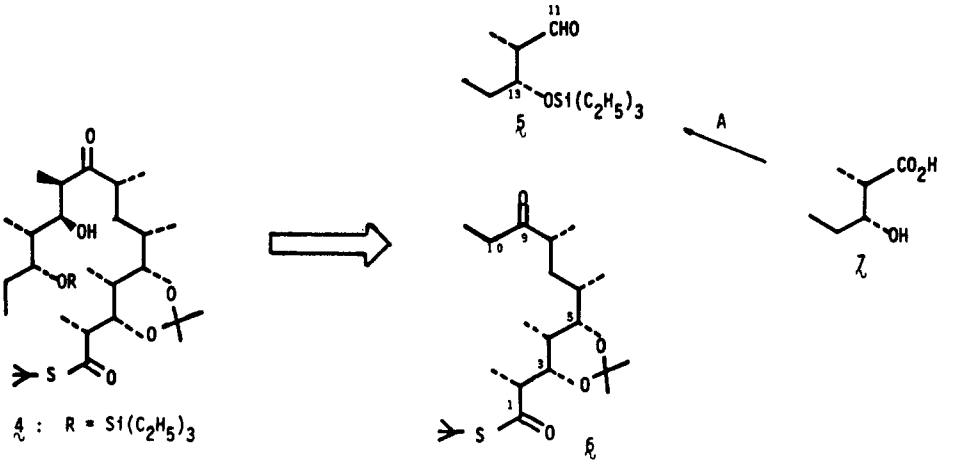
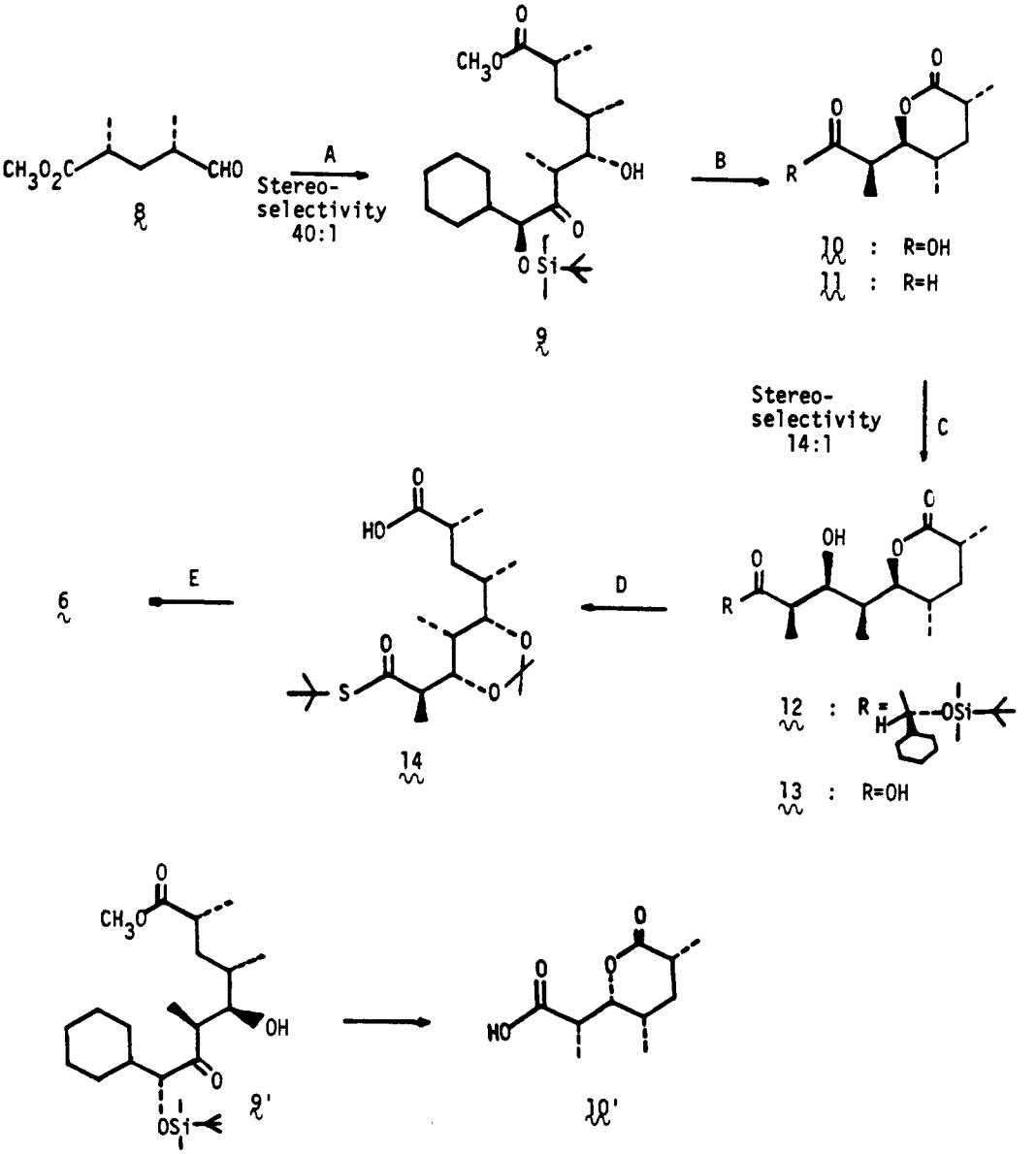
Scheme I[a]



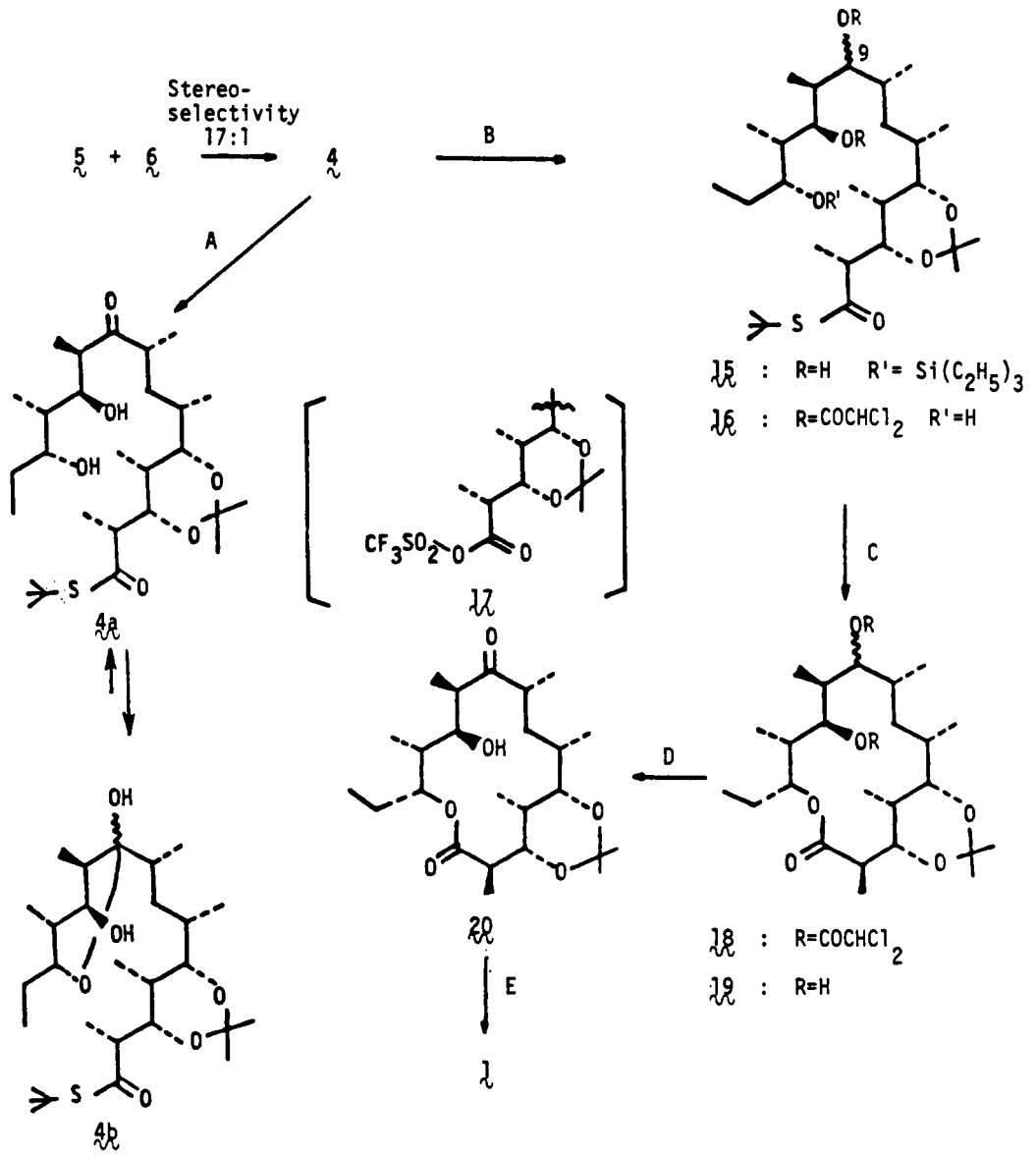
[a] (A) CH_2N_2; $(C_2H_5)_3SiCl$, *p*-$(CH_3)_2NC_5H_4N$ (CH_2Cl_2), room temperature; $(i\text{-}C_4H_9)_2AlH$ (hexane/ether), 0 °C; $CrO_3 \cdot 2C_5H_5N(CH_2Cl_2)$, 17 °C, 20 min.

Scheme II[b]



[b] (A) *S* reagent (hexane), 0 °C, 1.5 h. (B) concentrated HF–CH_3CN (1:20 v/v), room temperature, 3.5 h; $NaIO_4$ (CH_3OH/H_2O), room temperature, 1.5 h; **10** → **11**, $(COCl)_2$ (C_6H_6); H_2, 5% $Pd/BaSO_4$ + $[(CH_3)_2]_2CS$ $(C_6H_5CH_3)$, reflux. (C) *S* reagent (CH_2Cl_2), 0 °C, 1 h; **12** → **13**, $(n\text{-}C_4H_9)_4NF$ (THF), 0 °C, 30 min; $NaIO_4$ (CH_3OH/H_2O), room temperature, 2 h. (D) $ClCO_2C_2H_5 + C_5H_5N$ (THF), 0 °C, 1 h; TIS-*t*-C_4H_9 + *t*-C_4H_9SH, 0 °C → room temperature, 16 h; KOH $(H_2O/t\text{-}C_4H_9OH)$, 0 °C, 2 h; $(C_6H_5)_2$-*t*-C_4H_9SiCl (DMF); $CH_3C(OCH_3)=CH_2$ (CF_3CO_2H/CH_2Cl_2). (E) $(COCl)_2$, (C_6H_6), room temperature, 1 h; $LiCu(C_2H_5)_2$ (ether), −78 °C, 15 min.

Scheme III[a]



[a] (A) CH_3CO_2H (50%)/H_2O, room temperature, 1 h. (B) $NaBH_4$ (CH_3OH), -20 °C, 3 h; **15** → **16**, $(CHCl_2CO)_2O$ + C_5H_5N (CH_2Cl_2), 0 °C, 30 min; CH_3CO_2H (70%)/H_2O, room temperature, 16.5 h. (C) CuOTf + (2-C_3H_7)$_2NC_2H_5$ (C_6H_6), room temperature, 16 h; **18** → **19**, KOH (*t*-C_4H_9OH/THF/H_2O), room temperature, 1 h. (D) $C_5H_5NHCrO_3Cl$ + CH_3CO_2Na (CH_2Cl_2), room temperature, 2.5 h. (E) CF_3CO_2H (CH_3CN/H_2O), room temperature, 1 h.

hydroxy-2-methylcarbonyl system with a *selected* absolute configuration.[4]

Addition of the C_1–C_2 fragment to **10** again uses the *S*-chiral reagent. Aldol reaction of the aldehyde **11**[5] derived from **10** [$(COCl)_2$ and then Rosenmund reduction, 95% yield] provides the major product **12**[5] (stereoselection 14:1, 71% yield) and treatment with tetra-*n*-butylammonium fluoride followed by sodium metaperiodate converts **12** into carboxylic acid **13**[5] quantitatively. The functional groups of **13** are transformed through a series of reactions: conversion of **13** to its corresponding (*S*)-*tert*-butyl ester (1 equiv of C_2H_5OCOCl, C_5H_5N, TlS-*t*-C_4H_9),[9] lactone opening (0.95 equiv of KOH), protection of the carboxylic acid [$(C_6H_5)_2$-*t*-C_4H_9SiCl],[10] preparation of the acetonide from the diol [$CH_3C(OCH_3)$=CH_2, CF_3COOH], and finally desilylation [(*n*-$C_4H_9)_4NF$]. The resulting carboxylic acid **14**,[5] which is obtained in overall 46% yield after the above operations, has been found to be identical with the degradation product which represents the C_1–C_9 portion of **1**.[11] Further conversion of **14** into the corresponding ketone **6**[5] follows a conventional procedure [$(COCl)_2$, $LiCu(C_2H_5)_2$] and completes this simple and efficient synthesis of **6** (84% from **14**).

Seco-Acid Derivative 4. The final aldol condensation of both fragments **5** and **6** takes advantage of the expected coordination

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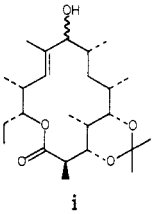
(11) The following sequence of reactions has been used to convert **1** into two fragments, **7** and **14**: (1) acetonide formation [$CH_3C(OCH_3)$=CH_2, CF_3CO_2H], (2) dehydration [$SOCl_2$ and C_5H_5N], (3) reduction of the ketone to compound i, (4) lactone opening [NaOH, $(CH_3)_2SO$, H_2O], (5) preparation



i

of the (*S*-*t*-C_4H_9 ester [$(C_2H_5O)_2POCl$, $(C_2H_5)_3N$, and then TlS-*t*-C_4H_9], and finally (6) double bond cleavage ($KMnO_4$–$NaIO_4$). This degradation was first performed by Dr. A. Ch. Greiner at the University of Alberta, Edmonton, Canada. We thank him for this contribution.

of the lithium cation (rather than boron) with the ethereal oxygen atom attached to the β carbon of aldehyde **5** (Cram's cyclic model).[12] Thus, treatment of **6** with *lithium bis(trimethylsilyl)amide*[13] at −78 °C followed by addition of **5** gives rise to the desired diastereoisomer **4**[5] in 88% yield and with a diastereoselection of 17:1, a result highly gratifying in view of the low selectivity (1.5–1.8:1) observed in our earlier boron-mediated condensations.[14] Since ratios ranging from 5–10:1 have been observed for the reactions of **5** with lithium enolates derived from achiral ketones such as 2-methyl-2-(trimethylsiloxy)penta-3-one, the above enhanced stereoselectivity must be due in part to the chirality of the C_8 center of **6**.[4] The synthesis of **4** thus proceeds in 11% overall yield based on (−)-aldehyde **8** and propionaldehyde used.

Lactonization. Desilylation of **4** (CH_3CO_2H–H_2O) yields the dihydroxy ketone **4a** which has been found to exist in equilibrium with the cyclic hemiketal **4b**. The equilibrium between **4a** and **4b** in solution strongly favors the latter and remains virtually unchanged upon preparation of various C_{11}-hydroxy derivatives. Since all attempts to lactonize the mixture of **4a** and **4b** were unsuccessful, it was necessary to make a synthetic detour via the C_9-hydroxy derivative **15**. Reduction of **4** with sodium borohydride gives a 1.4:1 mixture of the 9α- and 9β-hydroxy compounds (**15a,b**), which are separated. The low selectivity at this stage is of no consequence since both isomers are converted to **1** (Scheme III). Bisdichloroacetylation [$(Cl_2CHCO)_2O$, C_5H_5N] of **15a** and **15b** followed by desilylation (CH_3CO_2H) provides epimers **16a,b**, respectively, both of which are most efficiently lactonized with excess copper(I) trifluoromethanesulfonate[15] in benzene containing 2 equiv of diisopropylethylamine to neutralize the strong acid liberated during the reaction. Since the lactone formation proceeds with a delay relative to the disappearance of **16**, the mixed anhydride **17** serves as the probable intermediate in the overall lactonization process. The noticeable difference in the cyclization yield between **16a** and **16b** (41% from **16a** and 23% from **16b**)[16] may well be attributed to the differing conformation of these compounds. After the successful execution of this critical step, the ensuing transformations of **18a,b** via **19a,b** and **20**[5] proceed in a straightforward manner. Removal of the dichloroacetate protecting group (KOH) followed by selective oxidation of the C_9-hydroxy group[17] ($C_5H_5NHCrO_3Cl$, CH_3CO_2Na, CH_2Cl_2) and finally hydrolysis of the acetonide group (CF_3CO_2H, CH_3CN–H_2O) completes the total synthesis of 6-deoxyerythronolide B.

The above synthesis clearly demonstrates two distinct advantages of the aldol approach: (1) simplification of the synthetic design and (2) efficient creation of new chiral centers.

Acknowledgment. We thank Dr. A. O. Geiszler, Abbott Laboratories, for a generous gift of 6-deoxyerythronolide B, and the National Institutes of Health (Grant AI 15403) and Hoffmann-La Roche for generous financial support. D.S.G. is a National Cancer Institute Trainee (NCI Grant 2-T32-CA-09112-01). High-resolution mass spectra were provided by the facility, supported by the National Institute of Health (Grant RR 00317; principal investigator, Professor K. Biemann), from the Biotechnology Resources Branch, Division of Research Resources.

Supplementary Material Available: A listing of spectral data (8 pages). Ordering information is given on any current masthead page.

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(13) With this amide the (*Z*)-enolates are predominantly generated from ethyl ketones. See also: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(14) Masamune, S. *Pure Appl. Chem.*, in press.

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(17) Corey, E. J.; Melvin, L. S., Jr. *Tetrahedron Lett.* **1975**, 929.

Tritium Labeling of Organic Compounds by HNaY Zeolite Catalyzed Exchange with Tritiated Water and Their Analysis by ^{3}H NMR

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The activity of zeolite catalysts is promoted by small amounts of proton donors such as H_2O and HBr[1] (e.g., in alkylation reactions), but deactivation of the catalyst can be expected as H_2O to lattice AlO_4 ratios exceed unity. Thus D_2O is unsuitable as an isotope source for producing highly deuterated organics by zeolite-catalyzed exchange. However, the isotopic abundance typically required in tritium labeled organics, in contrast to the deuterated analogues, is relatively low. We now report that adequately tritiated compounds may indeed be produced very simply by exchange with small amounts of high specific activity tritiated water over HNaY zeolite.

The principle of using small amounts of high activity water in an otherwise "water-sensitive" catalytic system has previously been employed with Lewis acid labeling catalysts.[2,3] The advantages of such procedures include the relative simplicity of handling tritiated water and its low cost compared with alternatives such as tritium gas and tritiated benzene. No vacuum techniques are necessary, and the activity of the product is limited only by the specific activity of the small aliquot of HTO used as isotope source. The reactants, organic (0.1 g), zeolite (25 mg), and tritiated water (5 μL, 40 mCi/mL) were sealed in a glass ampule and heated to 175 °C for the desired reaction time. Products were analyzed by radiogas chromatography and ^{3}H NMR spectroscopy[4] (Table I). Since ^{3}H chemical shifts are yet to be extensively documented,[5] some shift measurements for particular assignments deduced from a consideration of the spectra of compounds labeled by a variety of exchange and synthetic procedures are included in Table I.

The results (Table I) show that the procedure represents a highly efficient method of tritiation of most aromatic compounds. Since the molar ratio of organic compound to water was high, equilibrium represents virtually 100% incorporation of the tritium utilized in the experiment. Only in the case of a severely deactivated aromatic (such as α,α,α-trifluorotoluene) or a bulky molecule (such as triphenylmethane or triphenylsilane) does exchange appear to be substantially hindered. The absence of exchange with bulky molecules is not surprising since the kinetic pore diameter of Y zeolite is ca. 8 Å.

The distribution of tritium within the aromatic nucleus as determined by ^{3}H NMR shows a marked preference toward ortho and para exchange for substituents which are typically ortho–para directing in electrophilic substitution. Similarly, naphthalene and furan exchange predominantly at the α carbon, while the halobenzenes exhibit a preference for para vs. ortho substitution as in nitration and chlorination. Likewise the relative exchange rates of aromatic compounds are similar to those found in common electrophilic substitution reactions, including hydrogen isotope exchange induced by mineral acids. The similarities of zeolite-

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