Asymmetric Synthesis of 2,3-Methanohomoserine: A General Approach to Chiral 2-Substituted Cyclopropane Amino Acids[1,2]

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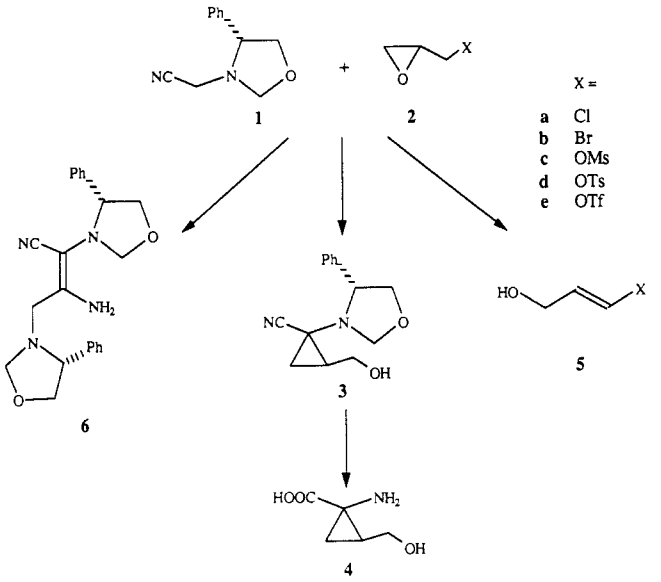
Double deprotonation-alkylation of the chiral aminonitrile synthon (*R*)-*N*-(cyanomethyl)-4-phenyloxazolidine (1) with LDA-HMPA and either epibromohydrin or glycidyl triflate gave in good yield the 2-(hydroxymethyl)cyclopropyl derivative in which two of the four possible diastereoisomeric forms predominated. A combination of simple chemical transformations of the cyclopropane C-1 substituents and chromatographic separation furnished two optically pure 2,3-methanohomoserines, functionalized as the methyl ester **11a** and the γ-lactone **10b**, respectively. These compounds can be converted into the free amino acids upon treatment with aqueous base and are proposed as useful intermediates in the asymmetric synthesis of other cyclopropane amino acids through subsequent manipulation of the 2-hydroxymethyl substituent.

Introduction

A considerable interest in cyclopropane amino acids has developed in recent years on account of the diverse biological activities exhibited by such species. The parent compound, 1-amino-1-cyclopropanecarboxylic acid (ACC), occurs naturally as the immediate biosynthetic precursor of the plant hormone ethylene[3] and also displays properties of pharmacological interest.[4] Two ACC derivatives bearing substituents at the cyclopropane C-2 are known to exist in Nature,[5,6] and a variety of other 2-substituted ACCs, sometimes referred to as 2,3-methano amino acids, have been prepared synthetically for use as mechanistic probes in ethylene biosynthesis studies[7] or for incorporation into oligopeptides in which they represent proteinogenic amino acids whose side chains have been effectively frozen in a particular conformation.[8] Such 2-substituted ACCs can exist in four possible stereoisomeric forms, and a variety of recent studies have demonstrated a high degree of stereochemical discrimination of ACC derivatives by biological systems.[7-9]

Three general strategies exist for the synthesis of functionalized ACCs: (a) cyclopropanation of functionalized α,β-dehydro amino acids,[6b,10] (b) Curtius or Hofmann rearrangements of appropriate cyclopropane 1,1-dicarboxylate derivatives,[7a,d,9c,11] and (c) double alkylation of glycine anion equivalents with 1,2-dielectrophiles.[7b,c,12] While many of the published synthetic routes exhibit a high degree of relative stereocontrol, i.e. control over the relative (cis or trans) disposition of the amino acid and the C-2 function, the products are invariably obtained as racemates, from which single enantiomers have to be separated by classical resolution techniques.[6b,11c,13] Despite

Scheme I



(1) Asymmetric Synthesis by the CN(*R,S*) Method; Part XIX. For Part XVIII, see: Zhu, J.; Quirion, J. C.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 5137.

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Table I. Results of Cyclopropanation Reactions in Scheme I[a]

entry	dielectrophile	yield of 3, %	recovered 1,[b] %
1	**2a**	4	84
2	**2a**[c]	9	81
3	**2b**[d]	45	45
4	**2b**[c]	55	45
5	**2b**[e]	4–25	35–45 (10–25)
6	**2c**	0	78
7	**2d**[d]	0	74
8	**2e**	65	25
9	**2b**[f]	80	8 (11)
10	**2e**[f]	75	3 (9)

[a] Standard reaction conditions are given in the Experimental Section. [b] Value in parentheses is the yield of dimer **6** which accompanied recovered 1. [c] Reaction time 6 h. [d] Identical yields were obtained when the reaction was repeated using either enantiomer of optically pure dielectrophile. [e] Reaction carried out without HMPA or with TMEDA instead of HMPA. [f] Only 1.05 equiv of LDA–HMPA was used to generate the anion; 1 h after addition of **2** a second 1.05 equiv of LDA–HMPA was added, and the reaction was held at −70 °C for a further 1 h before standard workup.

the clear requirement for enantiomerically pure materials for rigourous biological evaluation, only three genuine asymmetric syntheses have appeared in the literature to the present time.[7a,b,10e,14]

Results and Discussion

As part of our continuing program to develop convenient and general approaches for the asymmetric syntheses of natural products using chiral aminonitriles as building blocks, which we call the CN(*R*,*S*) method,[15] we recently reported[16] that (*R*)-*N*-(cyanomethyl)-4-phenyloxazolidine (**1**) can be alkylated or dialkylated at the aminonitrile function in reasonable diastereomeric excess through deprotonation of the aminonitrile center with strong base and reaction of the anion with simple electrophiles. We recognized this synthon as a chiral glycine equivalent[17] which could be used for the asymmetric synthesis of cyclopropane amino acids. The choice of the 1,2-dielectrophile for double alkylation was of prime importance, for we were concerned not only with stereoselective cyclopropanation of the chiral synthon but also in the generation of a derivative in which the 2-substituent could be transformed easily into other functional groups, thus providing a common route to a range of 2-substituted ACCs. On this rationale, and on the basis of earlier work,[18] we selected a dielectrophile having the general structure **2**, in order to generate a 2-(hydroxymethyl)cyclopropane derivative **3**, from which the first principal target would be 2-(hydroxymethyl)-ACC **4**, also known as 2,3-methanohomoserine[19] (Scheme I). The 1*R*,2*S* isomer of this compound has recently been shown to behave as an inhibitor of the ethylene-forming enzyme and is being investigated for use in affinity purification techniques and generation of antibodies.[7a]

Cyclopropanation Reactions. Initially, we examined a variety of racemic compounds **2** in a series of small scale reactions in which synthon **1** was allowed to react with the dielectrophile in the presence of 2.1 equivalents of LDA and HMPA. The results are shown in Table I (entries 1–8). The desired cyclopropane derivative **3** was obtained in yields which varied as a function of the leaving group X, with the best results being obtained using epibromohydrin **2b** and glycidyl triflate **2e**. Epichlorohydrin **2a** gave a lower yield than **2b**, as was anticipated for a poorer leaving group, but the total lack of reactivity of both the mesylate **2c** and tosylate **2d** was unexpected. In all cases, most of **1** that had not been transformed into **3** could be recovered from the reaction mixture.

Two features of this study aroused our curiosity and demanded a more detailed investigation. Specifically, we sought an explanation for the following: (a) while all the synthon could be accounted for at the end of a reaction, only up to 65% (entry 8) was alkylated, despite the presence of 1 full equiv of **2** and the necessary extra equivalent of base, and (b) the complete lack of reaction between the anion of **1** and **2c** or **2d**. A possible explanation was provided by reaction entry 7, from which, in addition to unreacted **1**, we isolated unreacted **2d** and a rearrangement product with structure **5d** (Scheme I). Strong base-induced β-deprotonation of epoxides followed by rearrangement to allyl alcohols has been documented in the literature[20] and is particularly favored by the use of LDA in the presence of HMPA.[20b] There is thus a depletion of both base and dielectrophile under the reaction conditions, and the maximum yield of **3** is clearly dependent on the remaining available **2d**. We noted, however, that after the standard reaction time (1 h) only 35% of **5d** had been formed, and 45% of the original **2d** still remained. Furthermore, when the reaction was carried out using either enantiomer of chiral **2d** the reagent was recovered without loss of optical activity, attesting to its integrity during the entire reaction period. We conclude that while a relatively slow base-induced rearrangement of **2d** does take place, the molecule has an inherent lack of reactivity with **1** under the prescribed conditions. Steric encumbrance of the large tosylate leaving group seems unlikely to be the explanation, in view of the analogous result obtained with the mesylate (entry 6). It may be that the strongly basic reaction medium effects deprotonation of both tosylate and mesylate methyl groups, giving stabilized anions resistant to nucleophilic attack.

We realized that the base-induced epoxide rearrangement might occur in reactions involving dielectrophiles other than **2d** and that this may have been the limiting factor in cases where cyclopropanation was otherwise clearly favourable, namely using **2b** and **2e**. To avoid this

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(14) Woodard has used a chiral bis(lactim ether) template to carry out stereoselective syntheses of C-2 deuterated ACCs but the method has not so far been extended to other 2-substituents: Subramanian, P. K.; Kalvin, D. M.; Ramalingam, K.; Woodard, R. W. *J. Org. Chem.* **1989**, *54*, 270. Schöllkopf's chiral bis(lactim ether) aminocarboxycarbene equivalent appears amenable to asymmetric synthesis of ACC derivatives but has so far been used only to prepare a meso-2,3-disubstituted ACC: Schöllkopf, U.; Haptreif, M.; Dippel, J.; Nieger, M.; Egert, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 192.

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(19) After submission of this full paper an asymmetric synthesis of (1*R*,2*S*)- and (1*S*,2*R*)-2-(hydroxymethyl)-ACCs was published (see ref 7a). Previously, a glycyl anion–dielectrophile strategy had been used to give a low yield of the cis isomer as a racemate only: Bland, J.; Shah, A.; Bortolussi, A.; Stammer, C. H. *J. Org. Chem.* **1988**, *53*, 992.

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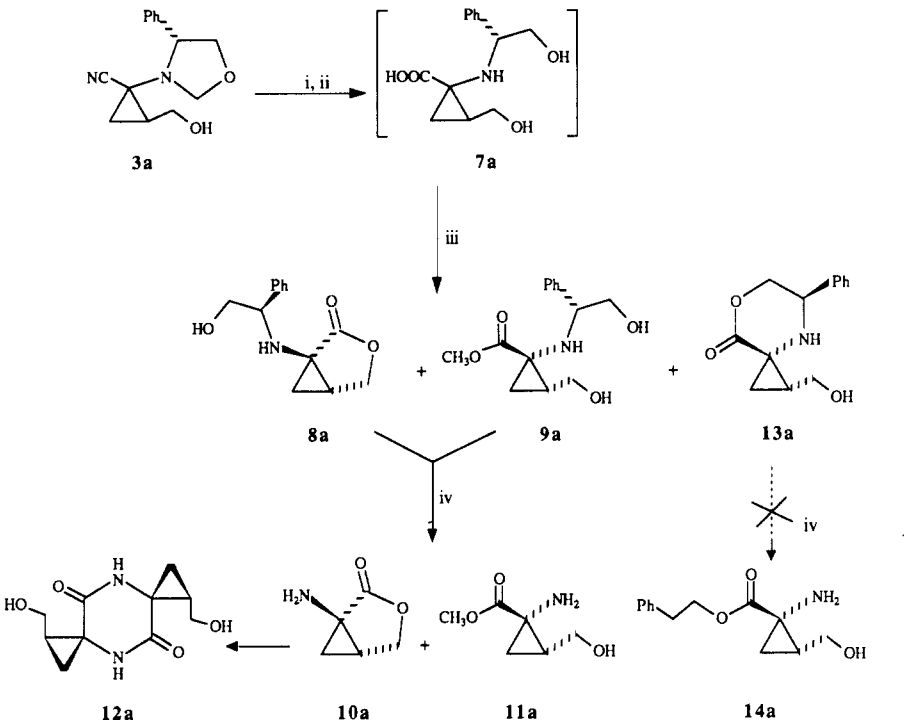
Scheme II[a]



[a] Structures are shown for the **a** series, derived from the less polar **3** pair; corresponding structures in the **b** series have the opposite configuration at both C-1 and C-2 cyclopropane stereocenters: (i) NaOH, Δ; (ii) H_3O^+, room temperature; (iii) $SOCl_2$, MeOH, Δ; (iv) H_2, Pd–C.

eventuality we repeated the reactions (entries 9 and 10) using only sufficient LDA–HMPA to generate the anion from **1**, to which was added the dielectrophile, followed 1 h later by a second equivalent of LDA–HMPA. In this way the best yield was improved to 80%. Although we were not able to demonstrate the formation of **5b** from **2b** in the experiment entry 3, we suspect that this was indeed the reason for the more modest yield of **3**; that we have been unable to detect any remaining **2b** by GLC at the end of the reaction time is further evidence in favor of this postulate.

We emphasize that the use of HMPA as a cosolvent for alkylations of **1** is essential. When no cosolvent is used, or if TMEDA is used instead of HMPA, the reaction with **2b** gives low and capricious yields of cyclopropane (entry 5). Furthermore, the yield of recovered **1** falls and a dimer of structure **6** is obtained (Scheme I). Dimerization of aminonitriles upon treatment with base has been reported previously[21,22] and appears to result when charge development onto the nitrile moiety of one molecule is not sufficient to prevent nucleophilic attack at its nitrile center by the anion of a second molecule. The use of HMPA suppresses formation of **6**, except when high yields of **3** are encountered (entries 9 and 10). The optimum conditions for dimer formation remain unclear, however, for treatment of **1** with LDA in the absence of both HMPA and an electrophile leads to **6** in only 10–15% yield.

With two new chiral centers, **3** can be produced in up to four stereoisomeric forms. Analysis of the ^{13}C NMR spectrum showed that four diastereomers were indeed present, but in unequal amounts, approximating to two major and two minor components (see Table II). The

Table II. ^{13}C NMR Resonance Values for Each Diastereoisomer of 3

	3a		3b	
atom	major 1*S*,2*R*	minor 1*R*,2*R*	major 1*S*,2*S*	minor 1*R*,2*S*
oxazolidine C2	85.6	85.1	85.5	86.6
C4	66.0	65.4	65.1	65.3
C5	74.3	74.1	74.3	74.0
aromatic	127.1	127.4	127.0	127.3
	127.9	128.3	127.7	128.1
	128.6	128.6	128.4	128.7
	139.8	139.3	139.4	139.7
cyclopropane C1	34.8	35.7	36.0	35.7
C2	28.4	29.0	28.9	29.6
C3	17.2	18.8	19.2	17.4
hydroxymethyl	59.5	61.2	61.6	59.1
nitrile	119.4	117.9	118.2	119.5

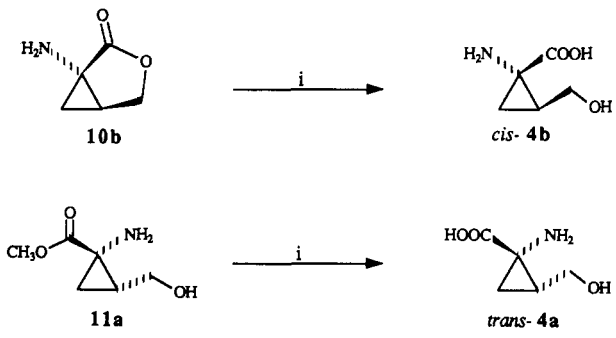
completely separated resonance signals from the hydroxymethyl carbon atoms (59.1, 59.5, 61.2, and 61.6 ppm) and the cyclopropane ring C-3s (17.2, 17.4, 18.8, and 19.2 ppm) were diagnostic in identification of each of the four components. The relative abundances (44:37:12:7), estimated from the peak heights of the abovementioned signals, were unvaried in all samples of **3**, regardless of the reaction yield and the identity of the dielectrophile used. We have performed the reaction with **2b** (entry 3) some 20 times with no more than 5% variation in the relative abundances. The significance of these figures is discussed below in the section on stereochemistry.

Conversion to Optically Pure Amino Acids. Our next task was 2-fold: to separate the four diastereomeric cyclopropanes and to convert their C-1 substituents into α-amino acid functions. Careful chromatography of the **3** mixture on silica gel allowed separation of two **3** pairs, each containing one major and one minor stereoisomer. That each pair comprised one component in which the 2-hydroxymethyl substituent was cis to the nitrile function and one in which these groups were trans was to our good

(21) (a) Padwa, A.; Eisenbarth, P.; Venkatramanan, M. K.; Wong, G. S. K.; *J. Org. Chem.* **1987**, *52*, 2427. (b) Stork, G.; Ozorio, A. A.; Leong, A. Y. W. *Tetrahedron Lett.* **1978**, 5178, note 3.

(22) Results obtained in this laboratory suggest that (diethylamino)-acetonitrile is prone to dimerization on treatment with LDA: Grierson, D. S., unpublished results.

Scheme III[a]



[a] (i) NaOH, room temperature.

fortune and was fully exploited in the subsequent chemical manipulation of the C-1 substituents to facilitate separation of the two components of each pair (Scheme II).

In a one-pot procedure the first 3 pair, designated **3a**, was treated sequentially with aqueous base then acid to hydrolyze the nitrile to a carboxylate and open the oxazolidine ring, to give hydroxy acid pair **7a**. Treatment with an anhydrous esterifying medium ($SOCl_2$–MeOH) induced γ-lactonization of the component having cis-disposed carboxylate and hydroxymethyl functions, giving **8a**, and intermolecular esterification with methanol for the trans isomer, yielding **9a**. This three-step procedure gave a good overall combined yield of **8a** and **9a** from **3a** (60–70%). Although **8a** and **9a** could be separated as single components at this stage, it was found more convenient to first remove the residual chiral appendage from the amino functions by hydrogenolysis of the mixture to give the primary amines **10a** and **11a**, which were finally separated by chromatography. Because the cis and trans components were not present in equal amounts in **3a**, the reaction sequence produced ester **11a** as the major product (46% overall from **3a**) while lactone **10a** was the minor product (2%). An analogous series of reactions performed on the second 3 pair, **3b**, yielded the corresponding enantiomeric structures **10b** and **11b**. In this case the major component was the lactone **10b** (28% from **3b**) while the ester **11b** was the minor one (7%). The γ-lactones **10a** and **10b** undergo spontaneous cyclodimerization at room temperature in a matter of days,[23] even without solvent, to give diketopiperazines **12a** and **12b**, respectively. This can be avoided by converting them, immediately after isolation, into their crystalline hydrochlorides which can be stored for long periods without decomposition.

By means of this series of simple chemical transformations and chromatographic separations all four stereomeric forms of 2-(hydroxymethyl)-ACC were made available, two of which were obtained in good yield. Although the two minor derivatives **10a** and **11b** were produced in the course of this synthetic scheme, the high degree of asymmetric induction at C-1 meant that they were obtained only in relatively small quantities. We suggest that a more practical means of obtaining these stereoisomers is to follow the synthetic scheme using the enantiomer of synthon **1** as the starting material. The synthesis of enantiomerically pure 2,3-methanohomoserines *cis*-**4b** and *trans*-**4a** was completed by basic hydrolysis of their respective precursors, followed by purification by ion-exchange chromatography and crystallization (Scheme III). The spectroscopic properties of these two amino acids are similar but not identical and are entirely consistent with

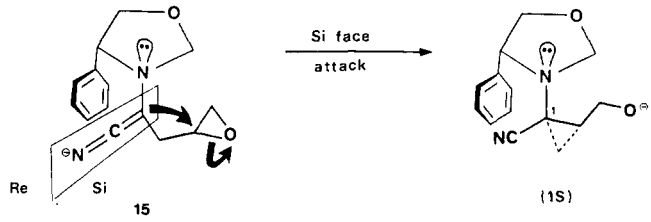


Figure 1. Preferred mode of intramolecular nucleophilic attack during cyclopropane ring closure.

their structures. The ^1H NMR spectra exhibit sufficient differences to facilitate distinction between the diastereoisomeric forms; the change in C-2 configuration in going from *trans*-**4a** to *cis*-**4b** deshields the *pro-S* proton at C-3 which moves downfield so that it almost coincides with the *pro-R* proton signal.

From each **3** pair one byproduct having structure **13** is obtained following the protocol of Scheme II. This results from δ-lactonization of the *trans*-hydroxy acid **7**, and is competitive with the intermolecular esterification. Only one such product is obtained from each **3** pair, as indicated by ^{13}C NMR spectroscopy, and that each originates from the trans derivative is evidenced by the concomitance of its appearance with the diminution in yield of esters **9** as a function of temperature during the second part of the hydrolysis procedure. In fact, by simply omitting the $SOCl_2$–MeOH step and heating the hydroxy acid mixture during the acid treatment, *cis*-/*trans*-**3** mixtures can be converted exclusively into **8**/**13** mixtures, albeit in reduced overall yield of the two components. This represented an alternative route to **4** in optically pure form, with **14** replacing **11** as the penultimate trans component, but both **13a** and **13b** turned out to be very stable to debenzylation conditions.[24] This structure therefore represents a synthetic "cul-de-sac", and we sought to minimize its formation in our experimental procedures. However its occurrence simplified the task of determining the absolute stereochemistry of our final products, as we now demonstrate.

Stereochemistry. Although convinced of the optical purity of products **4**, which was guaranteed by their separation in chemically or diastereomerically distinct forms, we required a means of deducing their absolute configurations. We assume that the dialkylation of **1** proceeds via a monoalkylated intermediate, which on deprotonation gives anion **15** (see Figure 1). In accordance with the working model which we developed[16] to explain the stereochemical results of simple alkylations of **1**, we predict a preferred conformation for **15** in which the epoxymethyl substituent and the phenyl group are on opposite sides of the plane defined by the aminonitrile anion, in order to minimize unfavorable steric interactions. In this conformation the second alkylation step will occur preferentially from the *Si*-face, leading to a 1*S* absolute configuration, *regardless* of the stereochemistry of the epoxymethyl stereocenter. This latter is dependent on the nature of the reagent **2**—racemic in routine experiments—thus we expect a mixture of 2*R* and 2*S* stereochemistries. The two major products *trans*-**4a** and *cis*-**4b** were derived from their respective **3** isomers without inversion, hence our model suggests their absolute stereochemistries to be 1*S*,2*R* and 1*S*,2*S*, respectively.

This postulate was proven by an X-ray study on the only convenient crystalline compound appearing in Schemes II and III, which was the δ-lactone byproduct **13a**. Sin-

(23) Homoserine lactone cyclodimerizes on standing in concentrated aqueous solution: Armstrong, M. D. *J. Am. Chem. Soc.* **1949**, *71*, 3399.

(24) Acid-catalyzed lactone alcoholysis (see ref 17a) of **13** simply represents a less direct route from *trans*-**3** to the same ester **9**.

gle-crystal analysis of this compound, details of which have been published elsewhere,[25] established its absolute stereochemistry as 1*S*,2*R*,7*R*. Since both **13a** and *trans*-**4a** were derived from the same single **3** isomer, the same 1*S*,2*R* stereochemistry can be assigned to the latter, in agreement with our model predictions.

Although a similar verification of the proposed 1*S*,2*S* configuration for *cis*-**4b** was not possible, the alternative 1*R*,2*R* configuration is highly improbable. Not only would it be in disaccord with model predictions and indicate no stereochemical induction at the alkylation center C-1 (in contrast with all previous results[16,26]), but it would require that *both* the major products *trans*-**4a** and *cis*-**4b** were formally derived from the same enantiomer of **2**. This would imply that either (a) synthon **1** exhibits a remarkable reagent stereoselection, reacting preferrentially with only one enantiomer of **2**, or that (b) the first alkylation step giving **15** proceeds with retention for one enantiomer of **2** and inversion for the other. These unlikely phenomena are effectively ruled out by the results of cyclopropanation reaction entry 3 using chiral **2b**. For both enantiomers of **2b** the reaction was C-2 stereospecific, in that only two of the four possible **3** isomers were produced, and by comparison of ^{13}C NMR spectra with those for the racemic series, it was deduced that the monoalkylation step proceeds by direct regiospecific S_N2 displacement of the halide.[27] We conclude with confidence that the product *cis*-**4b** is indeed the 1*S*,2*S* isomer.

Both the major cyclopropanes produced in the reaction sequence had a 1*S* configuration. The appearance of the two minor cyclopropanes attests to the stereoselective but not stereospecific nature of the alkylation reaction at C-1. Analysis of the ^{13}C NMR spectrum peak heights for typical **3** samples indicates that, as expected, there is approximately equal incorporation of each **2** enantiomer into the **3** mixture [average ratio (1*SR*,2*R*)-**3**:(1*SR*,2*S*)-**3** 51:49], but that there is a slight preference for **3** isomers with a trans configuration [average ratio (1*SR*,2*RS*)-**3**:(1*SR*,2*SR*)-**3** 56:44]. This latter figure merits some comment, for a number of literature preparations of racemic 2-substituted ACCs from nonchiral glycine equivalents have shown a high degree of *relative* stereochemical control, so that in some cases only one pair of enantiomers is obtained, either cis or trans depending on the type of glycine equivalent used. Although on first sight our purported asymmetric synthesis appears less selective, producing four stereomers despite the use of a chiral glycine equivalent, we emphasize that our system is exceptional in that it gives a high degree of *absolute* stereochemical control at C-1 (62% diastereomeric excess). The nature of the stereochemistry at C-2 is governed entirely by the preexisting stereocenter in the **2** reagent. Together these two factors dominate the stereochemical profile of the reaction, and any inherent cis/trans preference exerts only a minor influence.

Concluding Remarks

We have successfully carried out the synthetic transformations reported here on multigram scale on a routine basis using epibromohydrin as the dielectrophile. Whilst both **2b** and **2e** appear viable candidates for large-scale preparations, the choice of the former is based on practical considerations. Racemic epibromohydrin is available commercially and has a long shelf life. Glycidyl triflate, on the other hand, has to be prepared from glycidol, and is not stable for more than a few days even when stored at −20 °C;[28] indeed, it reacted visibly with solvent THF at room temperature during the 15-min addition time required in the alkylation reaction, which probably set the upper limit on the yield of **3**. The use of chiral **2b** as the dielectrophile may offer two advantages: (a) assuming that only one particular ACC stereomer is required, the yield of one or other of the major products *trans*-**4a** or *cis*-**4b** (depending on which **2b** enantiomer is used) can be doubled, and (b) it obviates the need for the first chromatographic separation procedure, which requires care and can be tedious on a large scale. We feel, however, that considerably more time and effort are spent on the preparation of the chiral reagent (requiring at least a five-step synthesis with only a modest overall yield[29]) than are necessary to effect satisfactory separation of the **3** pairs. Chiral epichlorohydrin, while perhaps more accessible,[30] is unfortunately too unreactive (entries 1 and 2) to replace epibromohydrin as the dielectrophile.

This work has furnished the asymmetric synthesis of one particular 2-substituted ACC, but it has much greater synthetic potential through the use of **10b** and **11a** as key chiral intermediates in the synthesis of others. The value of the hydroxymethyl side chain lies in its dual role in assisting the separation of diastereomeric components in the synthetic scheme and its ready subsequent chemical transformation to a variety of other functional groups, a study which is presently under investigation.

Experimental Section

Melting points were determined on a Reichert Thermovar apparatus and are uncorrected; 200-MHz ^1H and 50-MHz ^{13}C NMR spectra were recorded on a Bruker WP 200SY instrument. IR spectra were recorded on a Perkin-Elmer 297 instrument. Mass spectra were recorded on AEI MS 9 (CI) and MS 50 (EI) spectrometers. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Elemental analyses were carried out by the microanalytical service laboratory in the ICSN. TLC analyses were performed on silica gel GF 254 plates of 0.25 mm thickness, and components were visualized with a UV lamp and phosphomolybdate staining. Flash chromatography was done on 230–400-mesh silica gel (Merck). R_f values refer to TLC analysis using the same mobile phase reported for preparative separations, unless otherwise stated. Racemic epichlorohydrin and epibromohydrin were obtained commercially, distilled and stored over molecular sieves before use. Glycidyl triflate[28] and chiral epibromohydrin[29] were prepared according to literature procedures. All other reagents and solvents were obtained commercially and were dried and/or purified by standard procedures.

Cyclopropane 3. General Procedure. A solution of (*R*)-*N*-(cyanomethyl)-4-phenyloxazolidine (**1**),[16] (500 mg, 2.66 mmol) in THF (5 mL) was added dropwise over 0.5 h to a stirred solution of LDA [prepared from a 1.6 M solution of butyllithium in hexane (3.55 mL, 5.68 mmol) and diisopropylamine (0.80 mL, 5.71 mmol)] and HMPA (1.05 mL, 6.04 mmol) in THF (10 mL) at −70 °C under an atmosphere of dry nitrogen. After 0.5 h, the yellow anion solution was treated with a solution of dielectrophile **2** (2.79 mmol) in THF (5 mL) added dropwise over 0.25–0.5 h. Following a

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(26) (a) Marco, J. L.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 6345. (b) Marco, J. L.; Royer, J.; Husson, H.-P. *Synth. Commun.* **1987**, *17*, 669.

(27) The alternative mode of nucleophilic attack, i.e. initial epoxide opening (C-3 attack) followed by displacement of the halide to reestablish the oxirane ring, resulting in stereochemical inversion at C-2, did not occur. For discussions on the issue of C-1 versus C-3 regioselectivity, see: (a) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295. (b) McClure, D. E.; Arison, B. H.; Baldwin, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 3666.

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(30) A reviewer informs us that chiral epichlorohydrin is now available from Daiso Chemical Co.

further 1 h of stirring at −70 °C, 5 M ammonium chloride solution (3.5 mL) was added, and the mixture was allowed to warm to ambient temperature. The THF layer was collected and combined with dichloromethane washings (3 × 5 mL) of the residual aqueous layer. Organic extracts were dried over magnesium sulfate and concentrated, and the various components were separated by flash chromatography using 50:50 ethyl acetate–hexane. The four-component **3** mixture eluted as a pale yellow oil: R_f 0.35–0.43; IR (film) 3420 br, 2865, 2220, 1595 w, 755, 705 cm^{-1}; ^{13}C NMR ($CDCl_3$) see Table II; MS (EI) *m/e* 244 (M^+, 10), 213 (16), 199 (6), 183 (8), 169 (14), 156 (12), 130 (12), 123 (15), 104 (100), 93 (45), 91 (40). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.25; H, 6.69; N, 11.31.

From the experiment entry 7 was isolated tosylate **5d** as a pale yellow oil: R_f 0.19 (25:75 EtOAc–hexane); IR (film) 3360 br, 3050 w, 1670, 1605, 1370, 1190, 1180, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (br s, 1 H), 2.44 (s, 3 H), 4.07 (dd, 2 H, *J* = 6.1 and 1.5 Hz), 5.59 (dt, 1 H, *J* = 12.3 (d) and 6.1 (t) Hz), 6.64 (dd, 1 H, *J* = 12.3 and 1.5 Hz), 7.37 (d, 2 H, *J* = 8.3 Hz), 7.80 (d, 2 H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5 (q), 58.2 (t), 119.1 (d), 127.8 (d), 129.9 (d), 132.1 (s), 137.3 (d), 145.5 (s); MS (CI) *m/e* 229 (MH^+).

Separation of Cyclopropane 3 Pairs. Four-component **3** mixtures obtained by the above procedure gave single or overlapping spots on TLC analysis using a variety of solvent systems. Partial separation, giving two distinct spots of approximately equal staining intensity, was obtained with silica gel and 40:60 ethyl acetate–hexane. Flash chromatography of **3** using this system gave good, but not total, preparative-scale separation of these two two-component mixtures, designated **3a** (R_f 0.30) and **3b** (R_f 0.25). For a typical practical-scale separation a sample of **3** (4.40 g) was split into two portions and each was subjected to the above chromatographic treatment. The first third of the eluted **3** was pure **3a** and the final third pure **3b**. The middle fractions from both portions were combined and rechromatographed with the first and third bands eluting as single-spot material as before. Pooling of appropriate fractions gave **3a** (2.16 g) and **3b** (1.84 g) each as two-component single-spot samples. The remaining **3a/3b** mixture (0.27 g) can be subjected to further partial separation or can be combined with another large **3** sample for a future separation procedure.

Aminonitrile Dimer 6. A solution of **1** (250 mg, 1.33 mmol) in THF (5 mL) was added dropwise over 0.5 h to a stirred solution of LDA [prepared from a 1.6 M butyllithium solution in hexane (0.91 mL, 1.46 mmol) and diisopropylamine (0.22 mL, 1.57 mmol)] in THF (5 mL) at −70 °C under an atmosphere of dry nitrogen. After 0.5 h the reaction mixture was quenched with 5 M ammonium chloride solution (2.5 mL) and warmed to ambient temperature. Further workup was carried out as for the cyclopropanation reactions and flash chromatography using 30:70 ethyl acetate–hexane gave unreacted **1** (R_f 0.47; 74%) and dimer **6** (R_f 0.28; 7%). When the reaction was repeated and the anionic reaction medium allowed to warm to ambient temperature before the addition of ammonium chloride solution, the yield of **6** rose to 15%, but the recovery of **1** fell to only 40%. The dimer was further purified by preparative TLC and was obtained as a viscous pale brown oil: IR (film) 3460, 3330, 3050 m, 3020 m, 2180, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (d, 1 H, *J* = 14.4 Hz), 3.38 (d, 1 H, *J* = 14.4 Hz), 3.73 (dd, 2 H, *J* = 7.8 and 7.0 Hz), 3.87 (t, 1 H, *J* = 7.8 Hz), 3.93 (d, 1 H, *J* = 3.6 Hz), 4.11 (t, 1 H, *J* = 7.8 Hz), 4.19–4.26 (m, 3 H), 4.32 (t, 1 H, *J* = 7.8 Hz), 4.54 (d, 1 H, *J* = 2.8 Hz), 5.07 (br s, 2 H), 7.28–7.37 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 51.2 (t), 65.7, 67.3 (each d), 73.7 (t), 84.5, 86.5 (each t), 86.7 (s), 116.6 (s), 127.4, 127.5, 128.1, 128.6, 128.7 (each d), 138.6 (s), 155.8 (s); MS (EI) *m/e* 376 (M^+, 54), 345 (3), 255 (7), 240 (19), 237 (15), 197 (19), 162 (13), 148 (25), 121 (58), 103 (100), 91 (100).

Hydrolysis and Esterification of 3a. A solution of sodium hydroxide (1.45 g, 36.3 mmol) in water (45 mL) was added to **3a** (2.16 g, 8.84 mmol), and the mixture was heated under gentle reflux for 20 h and then cooled to 0 °C. The solution was taken to pH 2–3 with concentrated hydrochloric acid and stirred at ambient temperature for 20 h. The mixture was cooled to 0 °C, neutralized with 1 M sodium hydroxide, and then lyophilized. The dry residue was digested in methanol (65 mL), and the resulting suspension was stirred at 0 °C while thionyl chloride (1.3 mL, 17.8 mmol) was added slowly. When the addition was complete the mixture was allowed to warm, heated under reflux for 3 h, and then evaporated to dryness. The residual solids were treated with saturated aqueous sodium bicarbonate solution (50 mL) and organic products extracted with dichloromethane (3 × 75 mL). Extracts were dried over magnesium sulfate and concentrated to leave an oil which after flash chromatography using 80:20 ethyl acetate–hexane furnished the following compounds:

13a (0.21 g, 10% from **3a**) as white needles: R_f 0.48; mp 143–144 °C (EtOAc–hexane); $[\alpha]^{21}_D$ −23.7° (*c* 0.89, MeOH); IR (mull) 3500 sharp, 3280, 3080, 3050 w, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (dd, 1 H, *J* = 4.5 and 7.5 Hz), 1.49 (dd, 1 H, *J* = 4.5 and 10.1 Hz), 1.95–2.15 (m, 1 H), 3.05 (br s, 2 H), 3.61 (dd, 1 H, *J* = 8.6 and 11.9 Hz), 3.92 (dd, 1 H, *J* = 3.7 and 11.9 Hz), 4.30 (dd, 1 H, *J* = 10.4 and 3.4 Hz), 4.41 (t, 1 H, *J* = 10.4 Hz), 4.58 (dd, 1 H, *J* = 10.4 and 3.4 Hz), 7.32 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.0 (t), 30.1 (d), 40.8 (s), 55.3 (d), 59.9 (t), 74.8 (t), 126.5, 128.2, 128.8 (each d), 137.4 (s), 172.6 (s). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.83; H, 6.23; N, 6.04.

8a/9a mixture (1.63 g) as an oil, which was used without further separation: R_f 0.35 (faint) and 0.30 (intense); ^{13}C NMR ($CDCl_3$) δ (major ester **9a**) 17.2 (t), 29.7 (d), 43.4 (s), 52.0 (q), 60.1 (t), 63.9 (d), 67.0 (t), 127.3, 127.5, 128.2 (each d), 141.5 (s), 176.0 (s); δ (minor lactone **8a**) 18.7 (t), 24.2 (d), 43.4 (s), 62.3 (d), 66.6 (t), 68.1 (t), 128.2, 128.3, 128.6 (each d), 140.2 (s), 176.6 (s).

Hydrolysis and Esterification of 3b. The above procedure was repeated using **3b** (1.84 g, 7.53 mmol) and the other reagents on appropriate scale to give the following:

13b (0.19 g, 11% from **3b**) as an oil: R_f 0.48; $[\alpha]^{21}_D$ −55.0° (*c* 1.91, MeOH); IR (film) 3400 br, 3060, 3030, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (dd, 1 H, *J* = 4.0 and 6.5 Hz), 1.68 (dd, 1 H, *J* = 4.0 and 10.0 Hz), 1.73–1.86 (m, 1 H), 2.85 (br s, 2 H), 3.70 (dd, 1 H, *J* = 6.0 and 11.5 Hz), 3.99 (dd, 1 H, *J* = 2.5 and 11.5 Hz), 4.35–4.50 (m, 2 H), 4.63 (dd, 1 H, *J* = 10.0 and 2.5 Hz), 7.53 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.0 (t), 32.2 (d), 40.9 (s), 55.4 (d), 59.5 (t), 74.9 (t), 126.4, 128.2, 128.9 (each d), 137.3 (s), 171.6 (s). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.93; H, 6.23; N, 6.21.

8b/9b mixture (1.15 g) as an oil, which was used without further separation: R_f 0.28 (single spot); ^{13}C NMR ($CDCl_3$) δ (major lactone **8b**) 19.3 (t), 24.0 (d), 43.0 (s), 62.2 (d), 67.9 (t), 127.3, 127.4, 128.1 (each d), 140.7 (s), 177.6 (s); δ (minor ester **9b**) 16.5 (t), 30.5 (d), 42.6 (s), 51.4 (q), 59.2 (t), 63.4 (d), 65.0 (t), 127.3, 127.8, 128.3 (each d), 141.1 (s), 174.4 (s).

Alternative Hydrolysis of 3. A sample of four-component **3** (445 mg, 1.82 mmol) was treated with a solution of sodium hydroxide (325 mg, 8.13 mmol) in water (10 mL), and the mixture heated under gentle reflux for 24 h and then cooled to 0 °C. The solution was made pH 7 by addition of concentrated hydrochloric acid and was then lyophilized. The residue was digested in methanol (15 mL) and 1 M hydrochloric acid (3 mL) and then heated under reflux for 48 h. The mixture was concentrated, and the resulting slurry was diluted with water (25 mL) and made pH 7 by addition of saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with dichloromethane (4 × 25 mL), and the combined extracts were dried over magnesium sulfate and then concentrated to give a viscous brown oil, which after flash chromatography using 20:80 ethyl acetate–hexane yielded a **13a/13b** mixture (78 mg, 18%) and a **8a/8b** mixture (99 mg, 23%).

Debenzylation of 8a/9a Mixture. Active 10% palladium on charcoal (1.00 g) was added to a solution of **8a/9a** mixture (1.63 g) in methanol (175 mL), and the mixture was subjected to Parr hydrogenation at 30 psi overpressure for 20 h at ambient temperature. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated to give a solid–oil mixture. Flash chromatography using 10% methanol in ethyl acetate permitted separation of the 2-phenylethanol byproduct (R_f 0.77) and furnished the following:

Major ester **11a** (590 mg, 46% from **3a**) as a colorless oil: R_f 0.29; bp 110–115 °C (0.5 mm); $[\alpha]^{21}_D$ −38.4° (*c* 1.01, MeOH); IR (film) 3350 br, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (dd, 1 H, *J* = 4.7 and 7.3 Hz), 1.47 (dd, 1 H, *J* = 4.7 and 9.7 Hz), 1.75 (m, 1 H), 2.75 (br s, 3 H), 3.75 (s, 3 H), 3.85 (dd, 1 H, *J* = 12.0 and 5.2 Hz), 4.09 (dd, 1 H, *J* = 12.0 and 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.8 (t), 28.7 (d), 38.6 (s), 52.1 (s), 59.5 (t), 175.9 (s). Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.82; H, 7.71; N, 9.40.

Minor lactone **10a** (23 mg, 2% from **3a**) as a white solid, treated immediately with HCl–MeOH to give the hydrochloride: spectroscopic data as for major lactone hydrochloride **10b**.

Debenzylation of 8b/9b Mixture. The above procedure was repeated using the **8b/9b** mixture (1.15 g), 10% palladium on charcoal (0.75 g), and methanol (130 mL) to give the following:

Major lactone **10b** (240 mg, 28% from **3b**) as a white solid: R_f 0.21; mp 128 °C; converted immediately by treatment with HCl–MeOH to its hydrochloride, obtained as white needles: mp 164–166 °C dec ($CHCl_3$–MeOH); $[\alpha]^{21}_D$ +49.7° (*c* 0.94, MeOH); IR (mull) 3060 w, 1770 cm^{-1}; ^1H NMR (D_2O) δ 1.28 (t, 1 H, *J* = 5.0 Hz), 1.63 (dd, 1 H, *J* = 5.0 and 8.3 Hz), 2.72 (m, 1 H), 4.10 (d, 1 H, *J* = 8.5 Hz), 4.33 (dd, 1 H, *J* = 8.5 and 4.8 Hz); ^{13}C NMR (D_2O) δ 17.0 (t), 23.3 (d), 38.8 (s), 71.4 (t), 174.9 (s). Anal. Calcd for $C_5H_8ClNO_2$: C, 40.15; H, 5.39; N, 9.36. Found: C, 40.26; H, 5.35; N, 9.27.

Minor ester **11b** (80 mg, 7% from *3b*) as an oil: spectroscopic data as for major ester **11a**.

Cyclodimerization of 10b Free Base. A solid sample of major lactone **10b** free base obtained by the above procedure was dissolved in chloroform to give an approximately 1.5 M solution, which was set aside at ambient temperature for 10 days. Evaporation of the solvent left a quantitative yield of **12b**, as a white solid: R_f 0.15 (10% MeOH in EtOAc); mp >250 °C; $[\alpha]^{24}_D$ +103.8° (*c* 0.27, MeOH); IR (mull) 3270 br, 3160 sh, 1645 cm^{-1}; ^1H NMR (CD_3OD) δ 1.43 (dd, 1 H, *J* = 6.1 and 9.8 Hz), 1.61 (dd, 1 H, *J* = 6.1 and 7.6 Hz), 1.75 (m, 1 H), 3.44 (d, 1 H, *J* = 11.3 and 9.5 Hz), 3.90 (dd, 1 H, *J* = 11.3 and 5.3 Hz); ^{13}C NMR (CD_3OD) δ 14.3 (t), 32.9 (d), 41.9 (s), 60.3 (t), 172.2 (s); MS (CI) *m/e* 227 (MH^+).

(1*S*,2*R*)-2-(Hydroxymethyl)-ACC, *trans*-4a. A mixture of ester **11a** (105 mg, 0.723 mmol) and 1 M sodium hydroxide solution (1.5 mL) was stirred at ambient temperature for 4 h, chilled in an ice bath, acidified to pH 2 with concentrated hydrochloric acid, and then lyophilized. The resulting white solids were dissolved in a minimum of water, and the solution was applied to a 1 cm × 10 cm column of Amberlite IRN-77 cation exchange resin (H^+ form), which was eluted with water until the eluent was neutral. The product was then eluted with 1 M ammonium hydroxide solution (60 mL). Evaporation to dryness left a white powder, which on double recrystallization from H_2O–EtOH at 0 °C gave *trans*-**4a** (71 mg, 75%) as fine white needles: fragment violently >195 °C, mp 232–234 °C dec; $[\alpha]^{24}_D$ −71.6° (*c* 1.04, H_2O); ^1H NMR (D_2O) δ 1.14 (dd, 1 H, *J* = 6.2 and 7.0 Hz), 1.46 (dd, 1 H, *J* = 1.2 and 10.0 Hz), 1.77–1.94 (m, 1 H), 3.71 (dd, 1 H, *J* = 6.8 and 12.0 Hz), 3.94 (dd, 1 H, *J* = 5.2 and 12.0 Hz); ^{13}C NMR (D_2O) δ 16.3 (t), 25.7 (d), 40.6 (s), 59.8 (t), 176.7 (s). Anal. Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found: C, 44.91; H, 7.12; N, 10.41.

(1*S*,2*S*)-2-(Hydroxymethyl)-ACC, *cis*-4b. The above procedure was repeated using lactone hydrochloride **10b** (70 mg, 0.468 mmol) and 1 M sodium hydroxide solution (1.35 mL), and the crude product obtained as a fine white powder, recrystallized from H_2O–EtOH at −20 °C to give *cis*-**4b** (42 mg, 68%) as a clump of plates: sinter >150 °C to slender needles, mp 198–200 °C dec; $[\alpha]^{24}_D$ +23.3° (*c* 0.95, H_2O); ^1H NMR (D_2O) δ 1.38 (dd, 1 H, *J* = 10.2 and 6.5 Hz), 1.42 (t, 1 H, *J* = 6.5 Hz), 1.72–1.82 (m, 1 H), 3.75 (dd, 1 H, *J* = 11.5 and 7.2 Hz), 3.81 (dd, 1 H, *J* = 11.5 and 6.7 Hz); ^{13}C NMR (D_2O) δ 16.3 (t), 27.5 (d), 40.1 (s), 59.8 (t), 174.2 (s). Anal. Calcd for $C_5H_9NO_3 \cdot {}^1/_2H_2O$: C, 42.85; H, 7.19; N, 10.00. Found: C, 42.54; H, 6.99; N, 10.27.

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Registry No. 1, 101986-32-7; (±)-**2a**, 13403-37-7; (±)-**2b**, 82584-73-4; (*R*)-**2b**, 51594-57-1; (*S*)-**2b**, 96479-96-8; (±)-**2c**, 125876-09-7; (±)-**2d**, 118712-54-2; (±)-**2e**, 82337-76-6; (1*S*,2*R*)-**3**, 119066-45-4; (1*R*,2*R*)-**3**, 119066-46-5; (1*S*,2*S*)-**3**, 118970-47-1; (1*R*,2*S*)-**3**, 119066-44-3; *cis*-**46**, 125876-14-4; *trans*-**4a**, 125876-15-5; **5d**, 125830-44-6; **6**, 125830-45-7; **8a**, 119068-14-3; **8b**, 119068-17-6; **9a**, 114498-09-8; **9b**, 119066-47-6; **10a** (free base), 125876-11-1; **10a**·HCl, 119068-16-5; **10b** (free base), 125876-12-2; **10b**·HCl, 119068-15-4; **11a**, 114498-10-1; **11b**, 119066-43-2; **12a**, 125830-47-9; **12b**, 125876-13-3; **13a**, 125830-46-8; **13b**, 125876-10-0.

2-(((*p*-Nitrophenyl)sulfonyl)oxy)-3-keto Esters: Versatile Intermediates for the Preparation of 1,2,3-Tricarbonyl Compounds†

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The excellent leaving ability of the nosylate group and the high, differentiated functional group density in 2-(((*p*-nitrophenyl)sulfonyl)oxy)-3-keto esters, **1**, suggested that they might serve as versatile precursors for the synthesis of other 1,2,3-trifunctionalized compounds. Reaction of 2-(nosyloxy)-3-keto esters with triethylamine gives 1,2,3-tricarbonyl compounds in high yields. The tricarbonyl compound can be reacted, without isolation, with nucleophiles to give heterocyclic products in excellent yields.

Interest in 1,2,3-tricarbonyl compounds has risen dramatically in the last few years. The occurrence of this functionality in the powerful immunosuppressent FK-506[1] and related antibiotics[2] has led to several strategies for its incorporation into target structures.[3] In addition, Wasserman has elegantly demonstrated the valuable reactivity patterns of vicinal tricarbonyl compounds in the synthesis of a variety of heterocyclic systems.[4]

The best current methods for the introduction of the 1,2,3-tricarbonyl group include the singlet oxygen cleavage or ozonolysis of 2-enamino-3-keto esters,[4f] the ozonolysis of 2-iodoniumyl-3-keto esters,[5] the singlet oxygen cleavage or ozonolysis of 2-phosphorous ylide derivatives of 3-keto esters,[3] and the hydrolysis of 2-oximino-3-keto esters.[4e]

We have recently found that 2-(((*p*-nitrophenyl)-

† This paper is dedicated to Professor Ralph L. Dannley of Case Western Reserve University on the occasion of his 75th birthday.

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