Asymmetric Synthesis of β-Lactams. Highly Diastereoselective Alkylation of Chiral 2-Cyano Esters

Carlos Cativiela,* Maria D. Diaz-de-Villegas, and José A. Gálvez

Instituto de Ciencia de Materiales de Aragón, Departamento de Química Orgánica, Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain

Received August 9, 1993®

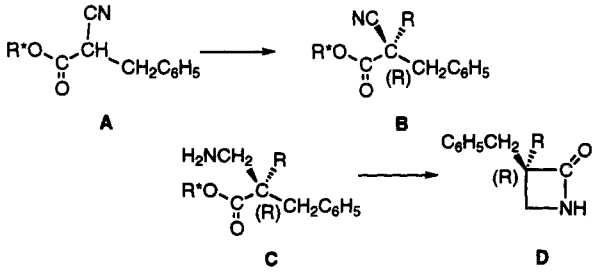
Enolates derived from 10-(dicyclohexylsulfamoyl)isobornyl 2-substituted-2-cyanoacetates were alkylated with very good yield and high diastereoselectivity. The reduction of the resulting reaction products and subsequent cyclization of the β-amino acids led to the corresponding β-lactam in high yields. This result paves the way for the development of a versatile and efficient asymmetric synthesis of enantiomerically pure (*R*)- and (*S*)-C(3)-disubstituted β-lactams.

Introduction

The discovery of the antibiotic activity of penicillins and cephalosporins constituted a breakthrough in the treatment of bacterial infections. The systematic chemical modification of natural lead structures has large precedent and has provided a large number of clinically-valuable β-lactam antibiotics, which have facilitated the development of modern medicine. However, problems of resistance and new therapeutic approaches require a continual supply and development of enantiomerically pure new compounds. Comparatively little work has been done on β-lactams with two alkyl substituents at C(3) although it is known[1] that these substances can act on the central nervous system.

One of the synthetic approaches to the β-lactam ring is *via* the cyclization of β-amino acids;[2] we have thus focused our attention on the diastereoselective synthesis of β-amino acids. Although several diastereoselective syntheses of β-amino acids and derivatives have been reported,[3] these compounds are often difficult to obtain in enantiomerically pure form.[4] As a consequence, the development of new methods providing a direct approach to β-amino acids which can be cyclized to β-lactams constitutes an area of active research.

In the course of our work on the synthesis of enantiopure β-lactams we first prepared (*R*)-3-alkyl-3-benzyl-2-azetidinones[5,6] starting from the chiral (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 3-phenyl-2-cyanopropanoate (**A**). Diastereoselective alkylation[7] of the enolate derived from **A** with activated halides led to (*2R*)-(*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-alkyl-3-phenyl-2-cyanopropanoates **B** with good yields and very high diastereoselectivities. These compounds can be converted into the corresponding chiral β-amino esters **C** which are subsequently cyclized to enantiopure β-lactams **D**.



Encouraged by the enormous potential of nonracemic C(3) disubstituted β-lactams, since they can act on the central nervous system,[1] we decided to explore the scope of this methodology in order to establish a general procedure for the preparation of (*R*)- or (*S*)-3,3-dialkyl(or 3-alkyl-3-aryl)-2-azetidinones.

Results and Discussion

Synthesis of starting materials. (*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-substituted-2-cyanoacetates **1–5** were prepared by different routes. (Scheme 1). (*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-cyano esters **1–3** were obtained in 88–91% yield by reaction of the corresponding acid chlorides with (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isoborneol in the presence of silver cyanide. The starting 2-alkyl-2-cyano acids were obtained by standard procedures. 2-Cyanopropanoic acid was obtained from 2-bromopropanoic acid by nucleophilic substitution reaction with sodium cyanide following the procedure of Lapworth and Baker.[8] 2-Cyanobutanoic acid and 3-methyl-2-cyanobutanoic acid were obtained by

® Abstract published in *Advance ACS Abstracts,* April 1, 1994.

(1) Testa, E.; Fontanella, L. *Ann.* **1959**, *625*, 95.

(2) (a) Kobayashi, S.; Imori, T.; Izawa, T.; Ohno, M. J. *J. Am. Chem. Soc.* **1981**, *103*, 2506. (b) Bachi, M. D.; Breiman, R.; Meshulam, H. *J. Org. Chem.* **1983**, *48*, 1439. (c) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.* **1984**, *49*, 1056. (d) Davies, S. G.; Dordor-Hedgecock, I.; Sutton, K. H.; Walker, J. C. *Tetrahedron Lett.* **1986**, *27*, 3787. (e) Kim, S.; Chang, S. B.; Lee, P. H. *Tetrahedron Lett.* **1987**, *28*, 2735. (f) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227. (g) Canielli, G.; Giacomini, D.; Panunzio, M.; Martelli, G.; Spunta, G. *Tetrahedron Lett.* **1987**, *28*, 3593. (h) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 613. (i) Kim, S.; Lee, P. H.; Lee, T. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1242. (j) Kunieda, T.; Nagamatsu, T.; Higuchi, T.; Hirobe, M. *Tetrahedron Lett.* **1988**, *29*, 2203.

(3) (a) Furukawa, M.; Okawara, T.; Terewaki, Y. *Chem. Pharm. Bull.* **1977**, *25*, 1319. (b) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 2223. (c) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112. (d) Brown, J. M.; James, A. P.; Prior, L. M. *Tetrahedron Lett.* **1987**, *28*, 2179. (e) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619. (f) Perlmutter, P.; Tabona, M. *Tetrahedron Lett.* **1988**, *29*, 949. (g) Potin, D.; Dumas, F.; d'Angelo, J. *J. Am. Chem. Soc.* **1990**, *112*, 3483. (h) Gmeiner, P. *Tetrahedron Lett.* **1990**, *31*, 5717. (i) Davies, S. G.; Dupont, J.; Easton, R. J. *Tetrahedron: Asymmetry* **1990**, *1*, 279. (j) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543. (k) Amoroso, R.; Cardillo, G.; Tomasini, C. *Tetrahedron Lett.* **1992**, *33*, 2725.

(4) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824.

(5) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1992**, *3*, 1141.

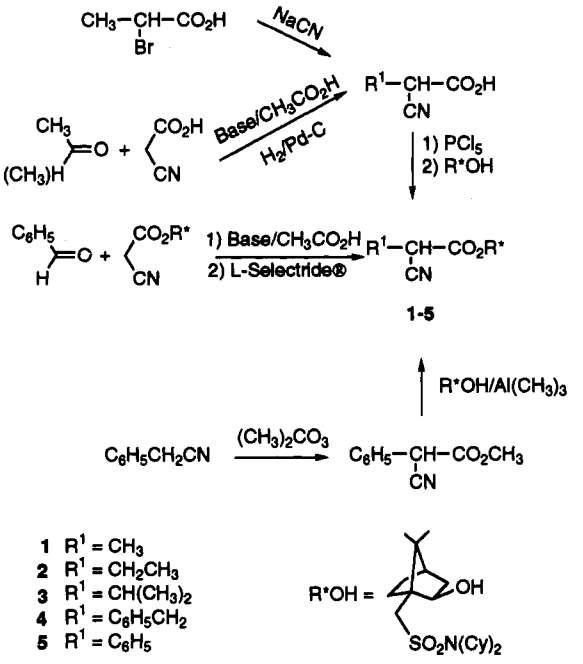
(6) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1993**, *4*, 229.

(7) For a recent review of diastereoselective alkylation of chiral enolates see: Aitken, R. A.; Kilenyi, S. N. *Asymmetric Synthesis*; Chapman and Hall: London, 1992; p 143.

(8) Lapworth, A.; Baker, W. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 181.

0022-3263/94/1959-2497$04.50/0

Scheme 1



Scheme 2

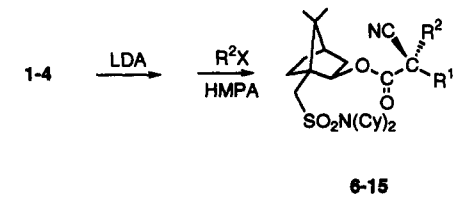


Table 1. Diastereoselectivity of Enolate Alkylations

entry	compound	R^1	R^2X	yield[a] (%)	dr	config C(α)
1	6	CH_3	CH_2=$CHCH_2Br$	93	81/19	*S*
2	7	CH_3	$C_6H_5CH_2I$	95	91/9	*S*
3	8	CH_3CH_2	CH_3I	96	80/20	*R*
4	9	CH_3CH_2	CH_2=$CHCH_2Br$	92	90/10	*S*
5	10	CH_3CH_2	$C_6H_5CH_2I$	95	94/6	*S*
6	11	$(CH_3)_2CH$	CH_3I	96	82/18	*R*
7	12	$(CH_3)_2CH$	CH_2=$CHCH_2Br$	95	93/7	*R*
8	13	$(CH_3)_2CH$	$C_6H_5CH_2I$	92	>98/2	*R*
9	14	$C_6H_5CH_2$	CH_3I	96	80/20	*R*
10	15	$C_6H_5CH_2$	CH_2=$CHCH_2Br$	96	91/9	*R*
11	16	C_6H_5	CH_3I	94	90/10	*S*
12	17	C_6H_5	CH_2=$CHCH_2Br$	92	>98/2	*S*
13	18	C_6H_5	$C_6H_5CH_2I$	91	>98/2	*S*
14	19	C_6H_5	CH_3CH_2I	90	>98/2	*S*

[a] Before recrystallization.

reductive Knoevenagel condensation of cyanoacetic acid with acetaldehyde or acetone, respectively, by a modification of the Cope's procedure.[9]

(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 3-phenyl-2-cyanopropanoate (**4**) was obtained by Knoevenagel condensation of (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)-isobornyl 2-cyanoacetate with benzaldehyde[10] and subsequent reduction of the (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyanocinnamate with L-selectride.[11] Finally (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-phenyl-2-cyanoacetate (**5**) was obtained by condensation of dimethyl carbonate with phenylacetonitrile[12] and subsequent transesterification of methyl 2-phenylcyanoacetate with (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)-isoborneol suitably activated by trimethylaluminum according to the transesterification procedure previously described by ourselves.[13]

Diastereoselective Alkylation. Diastereoselective alkylation of (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyano esters was performed by generation of the enolate with lithium diisopropylamide for 1 h in dry THF at low temperature followed by the addition of the corresponding alkyl halide in the presence of hexamethylphosphoramide (HMPA) (Scheme 2).

To determine the scope of the procedure we studied the enolate alkylation of (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyano esters with different substituents in C(2), as well as the influence of the alkyl halide in the alkylation reaction. In a previous study to this paper we examined the enolate alkylation of (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 3-phenyl-2-cyanopropanoate (**4**) with different alkyl halides and demonstrated[6] that our protocol was effective only for alkylations with activated alkyl halides such as benzylic halides, allylic halides, and methyl iodide. We therefore chose methyl iodide, allyl bromide, and benzyl iodide as alkylating agents and studied the alkylation reaction of substrates **1–5** with these reagents in all cases except those which give rise to a nonstereogenic center.

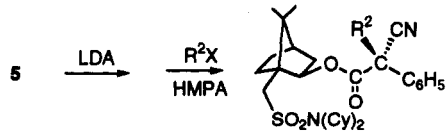
We first examined the enolate alkylation of (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-alkyl-2-cyanoacetates **1–4** with methyl iodide, allyl bromide, and benzyl iodide and in all cases observed the production of the corresponding alkylation product in excellent chemical yield and moderate to good diastereomeric excess (Table 1). The diastereomeric ratio of the products was determined in the crude reaction spectra by integration of the ^1H NMR (300 MHz) absorptions of the methine proton of esters when each diastereomer in the pair gave a separate doublet of doublets or by integration of the ^{13}C NMR (75 MHz) absorptions of the methine carbon.

The absolute configuration of the stereogenic center C(2) of compounds **7** and **14** was determined by hydrolysis in KOH/methanol which afforded (*S*)-2-methyl-3-phenyl-2-cyanopropanoic acid and (*R*)-2-methyl-3-phenyl-2-cyanopropanoic acid, respectively.[14] The absolute configuration of the stereogenic center C(2) of compound **8** was determined by correlation with that of (*R*)-2-amino-2-methylbutanoic acid obtained from it.[15] The absolute configuration of the stereogenic center C(2) of compounds **6**, **9–13**, and **15** was assigned on the basis of that of the final β-lactams.

We subsequently decided to study the enolate alkylation of 2-aryl-2-cyanoacetates and examined the reaction of (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyano-2-phenylacetate (**5**) with methyl iodide, allyl bromide, and benzyl iodide (Scheme 3). In all cases the corresponding alkylation product in excellent chemical yield and very high diastereoselectivity was obtained (Table 1). The

(9) Alexander, E. R.; Cope, A. C. *J. Am. Chem. Soc.* **1944**, *66*, 886.
(10) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Synth. Commun.* **1990**, *20*, 3145.
(11) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1657.
(12) Wallingford, V. H.; Jones, D. M.; Homeyer, A. H. *J. Am. Chem. Soc.* **1942**, *64*, 576.
(13) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Synthesis* **1990**, 198.
(14) $[\alpha]_D$ = +27.4°, c = 2.556 in $CHCl_3$ for the *S* enantiomer, Lee, K. K.; Terashima, S.; Achiwa, K.; Yamada, S. I. *Chem. Pharm. Bull.* **1969**, *17*, 2540.
(15) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1445.

Scheme 3



16-19

diastereomeric ratio of the methylation product was easily determined in the crude reaction spectra by integration of the ^1H NMR (300 MHz) absorptions of the methine proton of esters as each diastereomer in the pair gave a separate doublet of doublets. The allylation and benzylation products showed only one set of signals in both the ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra.

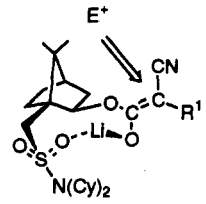
The absolute configuration of the stereogenic center C(2) of compound **16** was determined by hydrolysis in KOH/methanol which afforded (*S*)-2-phenyl-2-cyanopropanoic acid.[16] The absolute configuration of the stereogenic center C(2) of compound **17** was subsequently assigned on the basis of that of the final β-lactam and the absolute configuration of the stereogenic center C(2) of compound **18** was assigned by mechanistic considerations.

Chromatographic separation and recrystallization gave diastereomerically pure samples of C(2) dialkylated chiral cyano esters **6–18**.

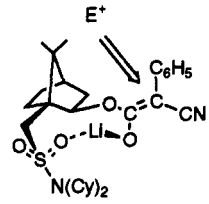
The absolute configuration at the stereogenic center C(2) of cyano esters **6–18** was easily directed in either sense by interchanging R^1 with R^2 (entries 2 and 9) as well as by using (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isoborneol or its antipode as the auxiliary. The latter option was demonstrated by the benzylation of (*1R,2S,4S*)-10-(dicyclohexylsulfamoyl)isobornyl 3-phenyl-2-cyanopropanoate.[5] One of the two strategies must be opted for taking into account the fact that R^2X must be an activated alkyl halide.

The only drawback with our synthetic protocol is when we wish to combine the phenyl and ethyl groups, since ethyl iodide is not an activated alkyl halide which usually causes a decrease in the reaction yields even when special conditions exist[17] as we have previously described for the addition of ethyl iodide to the enolate generated from (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyanopropanoate (**1**).[15] Nevertheless, when we tried the diastereoselective ethylation of the enolate generated from (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyano-2-phenylacetate (**5**) in the usual conditions, we obtained the desired alkylation product in high yield and diastereomeric ratio (entry 14). The absolute configuration of the stereogenic center C(2) of compound **19** was determined by hydrolysis in KOH/methanol which afforded (*S*)-2-phenyl-2-cyanobutanoic acid.[18]

Mechanistic Considerations. The observed reaction topicity in the alkylation of enolates derived from 2-alkyl-2-cyano esters **1–4** is consistent with formation of chelated (*Z*)-enolates **Z** and attack by the electrophile from the $C_{\alpha\text{-re}}$ face opposite to the 10-dicyclohexylsulfamoyl group. This parallels the results obtained in enolate-trapping reactions of enolates generated by conjugate addition.[11]



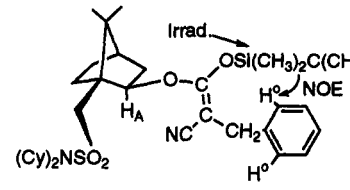
Z



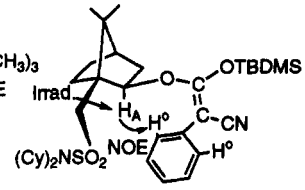
E

However the observed reaction topicity in the alkylation of enolates derived from 2-aryl-2-cyano ester **5** is consistent with the formation of chelated (*E*)-enolate **E** and attack by the electrophile from the $C_{\alpha\text{-si}}$ face opposite to the 10-dicyclohexylsulfamoyl group which is not in accordance with the previously proposed model.

In order to understand the observed stereochemical dichotomy between alkylation of enolates derived from 2-alkyl- and 2-aryl-2-cyano esters *O*-silyl enolates **Z-O** and **E-O** were isolated and their (*Z,E*) configuration was determined by ^1H NMR spectroscopy.



Z-O



E-O

In fact NMR nuclear Overhauser experiments on **E-O** showed that spin saturation of H_A caused a 1.9% enhancement of the H^O signal, whereas spin saturation of H_A on **Z-O** did not give any enhancement on benzylic protons which, on irradiation, did not increase the H_A signal either. Moreover, irradiation of the $SiCH_3$ signal slightly increased the H^O signal.

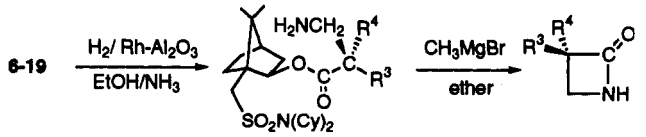
These results are in agreement with the (*E*)-configuration of the *O*-silyl enolate derived from 2-phenyl-2-cyano ester **5** and the (*Z*)-configuration *O*-silyl enolates derived from 2-alkyl-2-cyano esters **1–4**. This behavior is similar to that observed by Corey[19] in the formation of enolates derived from phenylacetic and alkylacetic allyl esters in the Ireland–Claisen rearrangement.

Hydrogenation and Subsequent Cyclization to Give the C(3) Disubstituted β-Lactams. The major diastereomers of alkylation were converted into the corresponding β-amino esters **20–32** in high yields by hydrogenation at 1 atm with rhodium on alumina of a solution of the precursor in 1% ammonia in ethanol (Scheme 4). Under these reaction conditions concomitant hydrogenation of the alkene moiety took place and the desired β-amino esters with a saturated substituent in C_2 were obtained in all cases except when both substituents have an aromatic ring. The results are summarized in Table 2.

Under usual conditions, hydrogenation of compound **18** did not take place and when we tried to promote this reaction at 45 °C and with a greater amount of catalyst, hydrogenolysis of the benzyl group and concomitant hydrogenation of the aromatic ring of the phenyl substituent took place.

(16) $[\alpha]^{20}_{578} = -9.0°$, in absolute ethanol for the *R* enantiomer, Knabe, J.; Urbahn, C. *Tetrahedron Lett.* **1970**, 2117.
(17) Baldwing, J. E.; Lee, V.; Schofield, J. C. *Synlett* **1992**, 249.
(18) $[\alpha]_D = -21.0°$, $c = 10\%$ in $CHCl_3$ for the *R* enantiomer, Cram, D. J.; Haberfield, P. *J. Am. Chem. Soc.* **1961**, *83*, 2354.
(19) Corey, E. J.; Duck-Hyung, L. *J. Am. Chem. Soc.* **1991**, *113*, 4026.

Scheme 4



20-32 33-45

Table 2. Reduction of Cyano Esters 6-19 to β-Amino Esters 20-32

compound	R^3	R^4	yield (%)
20	CH_3	$CH_3CH_2CH_2$	90
21	CH_3	$C_6H_5CH_2$	87
22	CH_3CH_2	CH_3	93
23	CH_3CH_2	$CH_3CH_2CH_2$	93
24	CH_3CH_2	$C_6H_5CH_2$	83
25	$(CH_3)_2CH$	CH_3	91
26	$(CH_3)_2CH$	$CH_3CH_2CH_2$	87
27	$(CH_3)_2CH$	$C_6H_5CH_2$	84
28	$C_6H_5CH_2$	CH_3	93
29	$C_6H_5CH_2$	$CH_3CH_2CH_2$	91
30	CH_3	C_6H_5	81
31	$CH_3CH_2CH_2$	C_6H_5	65
32	CH_3CH_2	C_6H_5	80

Table 3. Cyclization of β-Amino Esters 20-32 to β-Lactams 33-45

compound	R^3	R^4	yield (%)	config
33	CH_3	$CH_3CH_2CH_2$	96	*S*
34	CH_3	$C_6H_5CH_2$	90	*S*
35	CH_3CH_2	CH_3	96	*R*
36	CH_3CH_2	$CH_3CH_2CH_2$	95	*S*
37	CH_3CH_2	$C_6H_5CH_2$	91	*S*
38	$(CH_3)_2CH$	CH_3	96	*R*
39	$(CH_3)_2CH$	$CH_3CH_2CH_2$	87	*R*
40	$(CH_3)_2CH$	$C_6H_5CH_2$	94	*R*
41	$C_6H_5CH_2$	CH_3	89	*R*
42	$C_6H_5CH_2$	$CH_3CH_2CH_2$	86	*R*
43	CH_3	C_6H_5	92	*S*
44	$CH_3CH_2CH_2$	C_6H_5	94	*S*
45	CH_3CH_2	C_6H_5	92	*S*

The final step of the overall conversion of 2-cyano esters to β-lactams **33-45** is the cyclization of the β-amino esters **20-32** which was achieved with methylmagnesium bromide in ether (Scheme 4). A chromatographic separation allowed the isolation of enantiomerically pure β-lactams **33-45** and the recovery of the chiral auxiliary in high yields. The results are summarized in Table 3.

The absolute configuration of the β-lactams was established by comparing their CD curves with those of known isomers.[6]

Conclusion

We have developed a new, efficient, and general route to C(3) disubstituted β-lactams whose absolute configuration can be conveniently directed in the desired sense by correctly choosing the appropriate reagents.

Experimental Section

Apparatus. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FT IR infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity-300 spectrometer in deuteriochloroform using the solvent signal (δ 7.26 for ^1H and δ 77.0 for ^{13}C) as internal standard, and chemical shifts (δ) are given in parts per million and the coupling constants (J) in hertz. Mass spectra (MS) were determined on a high-resolution VG-Autospec spectrometer. Elemental analyses were performed with a Perkin-Elmer 2400 analyzer. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25 °C. Circular dichroism spectra were measured on a Jasco-720 spectropolarimeter.

Chemicals. All reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Lithium diisopropylamide (LDA) was generated in situ from diisopropylamine and butyllithium. Hexamethylphosphoric triamide and methylmagnesium bromide 3.0 M solution in ether were purchased from Aldrich Chemical Co. TLC was performed on Merck precoated silica gel plates which were visualized using UV light and anisaldehyde/sulfuric acid/ethanol (2/1/100). Flash column chromatography was performed using 230-400 mesh (Merck) silica gel.

2-Cyanopropanoic acid (prepared according to the literature procedure[8]): oil; IR (Nujol) 3500-2500, 2258, 1736 cm^{-1}; HRMS (EI) m/z = 99.0308 (M^+ calcd for $C_4H_5NO_2$ 99.0320); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (d, 3H, J = 6.6 Hz), 3.53 (c, 1H, J = 6.6 Hz), 10.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.9, 31.3, 116.8, 170.3.

2-Cyanobutanoic acid (prepared according to the literature procedure[9]): oil; IR (Nujol) 3500-2500, 2255, 1731 cm^{-1}; HRMS (EI) m/z = 113.0478 (M^+ calcd for $C_5H_7NO_2$ 113.0476); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10 (t, 3H, J = 7.5 Hz), 1.92-2.08 (m, 2H), 3.52 (t, 1H, J = 7.2 Hz), 7.40 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.1, 23.4, 38.9, 116.2, 170.0.

2-Cyano-3-methylbutanoic acid (prepared according to the literature procedure[9]): oil; IR (Nujol) 3500-2500, 2257, 1731 cm^{-1}; HRMS (EI) m/z = 127.0643 (M^+ calcd for $C_6H_9NO_2$ 127.0633); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (d, 3H, J = 6.9 Hz), 1.15 (d, 3H, J = 6.9 Hz), 2.38-2.48 (m, 1H), 3.47 (d, 1H, J = 5.1 Hz), 7.72 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3, 20.3, 29.5, 44.9, 114.9, 169.6.

Methyl 2-cyano-2-phenylacetate (prepared according to the literature procedure[12]): oil; IR (Nujol) 2250, 1752 cm^{-1}; HRMS (EI) m/z = 175.0635 (M^+ calcd for $C_{10}H_9NO_2$ 175.0633); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3H), 4.72 (s, 1H), 7.30-7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.5, 53.8, 115.4, 125.7, 127.9, 129.1, 129.3, 165.4.

General Procedure for the Synthesis of Cyano Esters 1-3. In a typical procedure the cyanoacyl chloride[20] (12 mmol) was added by means of a syringe to a stirred mixture of silver cyanide (1.206 g, 9 mmol) and (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isoborneol (2.382 g, 6 mmol) in toluene (60 mL) under argon and the mixture was heated at 80 °C for 4 h. The reaction mixture was then filtered, washed successively with a 10% aqueous sodium hydrogen carbonate solution and water, dried with magnesium sulfate, and concentrated in vacuo. Purification of the residue by flash chromatography on a silica gel column (eluent ether/hexane 1/3) afforded the corresponding 2-alkyl-2-cyano ester **1-3**.

(*2RS*)-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyanopropanoate (1). The general procedure was followed for the esterification of 1.386 g (12 mmol) of 2-cyanopropanoyl chloride to obtain 2.523 g (88% yield) of compound **1** as an equimolecular mixture of diastereomers: IR (Nujol) 2244, 1747 cm^{-1}; HRMS (FAB) m/z = 478.2869 (M^+ calcd for $C_{26}H_{42}N_2O_4S$ 478.2865); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 1.03 (s, 3H), 1.55 and 1.61 (d, 3H, J = 7.5 Hz), 1.00-2.00 (m, 27H), 2.59 and 2.62 (d, 1H, J = 13.5 Hz), 3.30 and 3.34 (d, 1H, J = 13.5 Hz), 3.14-3.30 (m, 2H), 3.49 (m, 1H, J = 7.5 Hz), 4.94-5.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.92 and 15.34, 19.84 and 19.88, 20.24, 25.14 and 25.19, 26.21 and 26.31, 26.37 and 26.41, 26.91 and 26.94, 30.55 and 30.73, 31.17 and 31.76, 32.24 and 32.49, 33.00 and 33.25, 39.05 and 39.07, 44.40 and 44.42, 49.27, 49.81 and 49.86, 53.77 and 53.95, 57.45 and 57.53, 80.29 and 80.62, 117.48 and 117.64, 165.08. Anal. Calcd for $C_{26}H_{42}N_2O_4S$: C, 65.24; H, 8.84; N, 5.85; S, 6.70. Found: C, 65.31; H, 8.93; N, 5.79; S, 6.73.

(*2RS*)-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyanobutanoate (2). The general procedure was followed for the esterification of 1.578 g (12 mmol) of 2-cyanobutanoyl chloride to obtain 2.686 g (91% yield) of compound **2** as an equimolar mixture of diastereomers: IR (Nujol) 2244, 1745 cm^{-1}; HRMS

(20) Ireland, E.; Chaykowsky, M. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 171.

(FAB) m/z = 492.2987 (M^+ calcd for $C_{27}H_{44}N_2O_4S$ 492.3021); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 3H), 0.96 and 0.97 (s, 3H), 1.02 and 1.07 (t, 3H, J = 7.2 Hz), 1.00–2.02 (m, 29H), 2.52 and 2.56 (d, 1H, J = 13.3 Hz), 3.10–3.24 (m, 2H), 3.26 (d, 1H, J = 13.3 Hz), 3.32–3.42 (m, 1H), 4.88–5.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.75 and 11.28, 19.64 and 19.66, 20.02 and 20.06, 23.02 and 23.26, 24.92 and 24.98, 26.01 and 26.07, 26.15 and 26.19, 26.72, 30.34 and 30.48, 31.99 and 32.20, 32.86 and 33.04, 38.44, 38.98 and 39.05, 44.15 and 44.21, 49.03 and 49.04, 49.49 and 49.58, 53.43 and 53.63, 57.17 and 57.25, 80.05 and 80.15, 116.33 and 116.42, 164.27 and 164.34. Anal. Calcd for $C_{27}H_{44}N_2O_4S$: C, 65.82; H, 9.00; N, 5.68; S, 6.51. Found: C, 65.74; H, 8.82; N, 5.83; S, 6.42.

(2*RS*)-(1*S*,2*R*,4R)-10-(Dicyclohexylsulfamoyl)isobornyl 3-Methyl-2-cyanobutanoate (3). The general procedure was followed for the esterification of 1.746 g (12 mmol) of 2-cyano-3-methylbutanoyl chloride to obtain 2.702 g (89% yield) of compound **3** as an equimolar mixture of diastereomers: IR (Nujol) 2245, 1744 cm^{-1}; HRMS (FAB) m/z = 506.3166 (M^+ calcd for $C_{28}H_{46}N_2O_4S$ 506.3178); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H), 1.02 and 1.05 (s, 3H), 1.12 (d, 6H, J = 6.6 Hz), 1.05–2.03 (m, 27H), 2.47 (m, 1H, J = 6.6 Hz), 2.60 and 2.62 (d, 1H, J = 13.2 Hz), 3.18–3.36 (m, 3H), 3.31 and 3.40 (d, 1H, J = 13.2 Hz), 5.98–6.14 (dd, 1H, J = 7.5 Hz, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.04, 19.96, 20.30 and 20.37, 20.78 and 20.91, 25.15 and 25.24, 26.29, 26.40 and 26.45, 26.96, 29.43 and 29.66, 30.60 and 30.69, 32.20 and 32.42, 33.19 and 33.31, 39.26 and 39.48, 44.36 and 44.49, 45.07 and 45.58, 49.29 and 49.34, 49.61 and 49.90, 53.59 and 53.88, 57.39 and 57.53, 80.30 and 80.57, 116.53, 164.18. Anal. Calcd for $C_{28}H_{46}N_2O_4S$: C, 66.37; H, 9.15; N, 5.53; S, 6.32. Found: C, 66.29; H, 9.02; N, 5.61; S, 6.40.

(2*RS*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 3-phenyl-2-cyanopropanoate (4) (prepared according to the procedure previously described by ourselves[10,11]): IR (Nujol) 2251, 1749 cm^{-1}; HRMS (FAB) m/z = 554.3181 (M^+ calcd for $C_{32}H_{46}N_2O_4S$ 554.3178); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 and 0.86 (s, 3H), 0.80 and 1.01 (s, 3H), 1.02–2.00 (m, 27H), 2.58 and 2.64 (d, 1H, J = 13.5 Hz), 3.10–3.45 (m, 5H), 3.62 and 3.78 (dd, 1H, J = 5.4 and 4.5 Hz, J = 9.9 and 7.8 Hz), 5.00 and 5.04 (dd, 1H, J = 7.8 Hz, J = 3.3 Hz), 7.25–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.64 and 19.93, 20.23 and 20.29, 25.19, 26.28 and 26.41, 26.95, 30.57 and 30.89, 32.34 and 32.42, 33.15 and 33.28, 35.31 and 35.96, 38.84 and 39.13, 39.44 and 40.10, 44.42, 49.24 and 49.33, 49.83 and 49.93, 53.92 and 53.98, 57.54, 80.55 and 80.61, 116.41 and 116.47, 127.56 and 127.70, 128.71 and 128.83, 128.86 and 129.27, 135.25 and 136.05, 164.11 and 164.22. Anal. Calcd for $C_{32}H_{46}N_2O_4S$: C, 69.28; H, 8.36; N, 5.05; S, 5.78. Found: C, 69.21; H, 8.42; N, 5.11; S, 5.83.

(2*RS*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Phenyl-2-cyanoacetate (5). In a dried, argon-filled two-neck round-bottomed flask fitted with stirrer, reflux condenser, and suba-seal septum joint was dissolved (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isoborneol (3.176 g, 8 mmol) in anhydrous toluene (50 mL), and a solution of trimethylaluminum 2.0 M in hexanes (4.8 mL, 9.6 mmol) was added. The solution was stirred at room temperature for 30 min and then a solution of methyl 2-cyano-2-phenylacetate[12] (1.824 g, 10.4 mmol) in toluene (15 mL) was added through a suba-seal septum at a moderate rate. The solution was stirred at 80 °C for 8 h. The reaction mixture was quenched by addition of solid $Na_2CO_3 \cdot 10H_2O$ (3 g) and filtered. Evaporation of the solvent in vacuo afforded the crude product **5** which was chromatographed on a silica gel column (230–400 mesh) eluting with ether/hexane 1/2 to afford 4.017 g (93%) of compound **5** as an equimolecular mixture of diastereomers: IR (Nujol) 2250, 1747 cm^{-1}; HRMS (FAB) m/z = 540.2985 (M^+ calcd for $C_{31}H_{44}N_2O_4S$ 540.3021); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 and 0.87 (s, 3H), 0.84 and 1.06 (s, 3H), 1.02–2.00 (m, 27H), 2.63 and 2.66 (d, 1H, J = 13.2 Hz), 3.20–3.40 (m, 2H), 3.32 (d, 1H, J = 13.2 Hz), 4.67 and 4.72 (s, 1H), 5.04 and 5.08 (dd, 1H, J = 7.8 Hz, J = 3.0 Hz), 7.32–7.52 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.72 and 20.30, 19.98 and 20.30, 25.21 and 25.27, 26.33 and 26.41, 26.51 and 26.53, 26.93 and 26.97, 30.66 and 30.76, 32.37 and 32.42, 33.26 and 33.39, 38.88 and 39.15, 43.37 and 43.63, 44.41 and 44.44, 49.25 and 49.35, 49.88 and 50.14, 53.90 and 54.07, 57.49, 80.69 and 81.11, 115.97, 125.72, 127.91 and 128.43, 120.04 and 129.24, 130.56, 163.40. Anal. Calcd for $C_{31}H_{44}N_2O_4S$: C, 68.85; H, 8.20; N, 5.18; S, 5.93. Found: C, 68.93; H, 8.22; N, 5.23; S, 5.86.

General Procedure for Enolate Alkylation. To a dry THF solution (25 mL) of lithium diisopropylamide, generated in situ from diisopropylamine (120 mg, 1.2 mmol) and butyllithium (1.1 mmol), under argon at −78 °C, was added a solution of the corresponding 2-cyano ester **1–5** (1 mmol) in dry THF (5 mL). After 1 h a solution of the corresponding alkyl halide (10 mmol) and HMPA (270 mg, 1.5 mmol) in dry THF (5 mL) was added by syringe. The reaction mixture was allowed to warm to room temperature and stirring was continued for 1 day. The mixture was then quenched with saturated aqueous NH_4Cl solution (5 mL). An ether extraction, washing by water, drying on $MgSO_4$ and concentration in vacuo yielded a mixture of diastereomers of the corresponding α-dialkylated 2-cyano ester **6–19** as a crude oil, which was chromatographed on a silica gel column (eluent ether/hexane 1/4). Recrystallization from hexane afforded enantiomerically pure samples of compounds in most cases.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2-methyl-4-pentenoate (6). The general procedure was followed for the alkylation of 478 mg (1 mmol) of **1** with 1.21 g (10 mmol) of CH_2CHCH_2Br. Purification of the crude product by flash chromatography and recrystallization afforded 290 mg (56% yield) of diastereomerically pure **6**: mp 154 °C; IR (Nujol) 2247, 1739 cm^{-1}; HRMS (FAB) m/z = 518.3144 (M^+ calcd for $C_{29}H_{46}N_2O_4S$ 518.3178); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 1.05 (s, 3H), 1.62 (s, 3H), 1.00–2.05 (m, 27H), 2.45 (dd, 1H, J = 13.8 Hz, J = 7.2 Hz), 2.60 (d, 1H, J = 13.5 Hz), 2.63 (dd, 1H, J = 13.8 Hz, J = 7.2 Hz), 3.20–3.36 (m, 2H), 3.40 (d, 1H, 13.5 Hz), 4.98 (dd, 1H, J = 7.8 Hz, J = 2.7 Hz), 5.16–5.28 (m, 2H), 5.74–5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9, 20.3, 22.9, 25.2, 26.2, 26.4, 27.0, 30.7, 32.2, 33.4, 39.3, 42.6, 43.5, 44.4, 49.3, 49.8, 53.7, 57.4, 80.4, 119.9, 120.9, 130.7, 167.8. Anal. Calcd for $C_{29}H_{46}N_2O_4S$: C, 67.14; H, 8.94; N, 5.40; S, 6.18. Found: C, 67.03; H, 8.85; N, 5.33; S, 6.27.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2-methyl-3-phenylpropanoate (7). The general procedure was followed for the alkylation of 478 mg (1 mmol) of **1** with 2.18 g (10 mmol) of $C_6H_5CH_2I$. Purification of the crude product by flash chromatography and recrystallization afforded 365 mg (64% yield) of diastereomerically pure **7**: mp 220 °C; IR (Nujol) 2240, 1743 cm^{-1}; HRMS (FAB) m/z = 568.3387 (M^+ calcd for $C_{33}H_{48}N_2O_4S$ 568.3334); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.51 (s, 3H), 0.74 (s, 3H), 1.74 (s, 3H), 1.00–1.80 (m, 27H), 2.48 (d, 1H, J = 13.2 Hz), 2.98 (d, 1H, J = 13.2 Hz), 3.15 (d, 1H, 13.2 Hz), 3.20–3.34 (m, 2H), 3.29 (d, 1H, J = 13.2 Hz), 4.87 (dd, 1H, J = 7.8 Hz, J = 3.0 Hz), 7.26–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 20.2, 23.8, 25.2, 26.2, 26.4, 26.9, 30.7, 32.1, 33.4, 38.5, 44.3, 44.5, 45.8, 49.1, 49.7, 53.7, 57.4, 80.0, 120.3, 127.8, 128.4, 130.0, 134.4, 167.6. Anal. Calcd for $C_{33}H_{48}N_2O_4S$: C, 69.68; H, 8.51; N, 4.92; S, 5.64. Found: C, 69.74; H, 8.46; N, 5.01; S, 5.58.

(2*R*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2-methylbutanoate (8). The general procedure was followed for the alkylation of 492 mg (1 mmol) of **2** with 1.42 g (10 mmol) of CH_3I. Purification of the crude product by flash chromatography and recrystallization afforded 265 mg (52% yield) of diastereomerically pure **8**: mp 133 °C; IR (Nujol) 2253, 1739 cm^{-1}; HRMS (FAB) m/z = 506.3169 (M^+ calcd for $C_{28}H_{46}N_2O_4S$ 506.3178); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H), 1.05 (s, 3H), 1.14 (t, 3H, J = 7.2 Hz), 1.53 (s, 3H), 1.00–2.20 (m, 29H), 2.59 (d, 1H, J = 13.5 Hz), 3.18–3.32 (m, 2H), 3.37 (d, 1H, J = 13.5 Hz), 4.97 (dd, 1H, J = 7.8, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.5, 19.8, 20.2, 22.9, 25.0, 26.1, 26.2, 26.8, 30.5, 30.5, 31.9, 33.3, 39.3, 44.2, 44.3, 49.2, 49.5, 53.4, 57.3, 80.0, 119.9, 167.9. Anal. Calcd for $C_{28}H_{46}N_2O_4S$: C, 66.37; H, 9.15; N, 5.53; S, 6.32. Found: C, 66.43; H, 9.06; N, 5.62; S, 6.33.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2-ethyl-4-pentenoate (9). The general procedure was followed for the alkylation of 492 mg (1 mmol) of **2** with 1.21 g (10 mmol) of CH_2CHCH_2Br. Purification of the crude product by flash chromatography and recrystallization afforded 330 mg (62% yield) of diastereomerically pure **9**: mp 124 °C; IR (Nujol) 2244, 1737 cm^{-1}; HRMS (FAB) m/z = 532.3338 (M^+ calcd for $C_{30}H_{48}N_2O_4S$ 532.3334); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 1.03 (s, 3H), 1.12 (t, 3H, J = 7.5 Hz), 1.00–2.20 (m, 29H),

2.50–2.58 (m, 2H), 2.57 (d, 1H, J = 13.2 Hz), 3.22–3.36 (m, 2H), 3.38 (d, 1H, 13.2 Hz), 4.94 (dd, 1H, J = 7.8, J = 3.0 Hz), 5.15–5.26 (m, 2H), 5.74–5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.6, 19.9, 20.3, 25.2, 26.2, 26.4, 27.0, 29.9, 30.7, 32.1, 33.5, 39.5, 41.4, 44.4, 49.3, 49.6, 49.7, 53.5, 57.3, 80.7, 119.0, 120.8, 130.8, 167.4. Anal. Calcd for $C_{30}H_{48}N_2O_4S$: C, 67.63; H, 9.08; N, 5.26; S, 6.02. Found: C, 67.59; H, 9.06; N, 5.31; S, 5.96.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Benzyl-2-cyanobutanoate (10). The general procedure was followed for the alkylation of 492 mg (1 mmol) of **2** with 2.18 g (10 mmol) of $C_6H_5CH_2I$. Purification of the crude product by flash chromatography and recrystallization afforded 395 mg (68% yield) of diastereomerically pure **10**: mp 145 °C; IR (Nujol) 2254, 1740 cm^{-1}; HRMS (FAB) m/z = 582.3465 (M$^+$ calcd for $C_{34}H_{50}N_2O_4S$ 582.3491); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.37 (s, 3H), 0.72 (s, 3H), 1.20 (t, 3H, J = 7.5 Hz), 1.00–2.20 (m, 29H), 2.45 (d, 1H, J = 13.2 Hz), 3.06 (s, 2H), 3.18–3.36 (m, 2H), 3.26 (d, 1H, 13.2 Hz), 4.79 (dd, 1H, J = 7.8, J = 3.0 Hz), 7.26–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.7, 19.3, 20.2, 25.2, 26.2, 26.4, 26.9, 30.6, 31.0, 31.9, 33.6, 38.9, 42.9, 44.3, 49.1, 49.4, 51.9, 53.4, 57.3, 80.5, 119.3, 127.7, 128.4, 130.2, 134.3, 167.3. Anal. Calcd for $C_{34}H_{50}N_2O_4S$: C, 70.06; H, 8.65; N, 4.81; S, 5.50. Found: C, 69.97; H, 8.58; N, 4.87; S, 5.46.

(2*R*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2,3-dimethylbutanoate (11). The general procedure was followed for the alkylation of 506 mg (1 mmol) of **3** with 1.42 g (10 mmol) of CH_3I. Purification of the crude product by flash chromatography and recrystallization afforded 260 mg (50% yield) of diastereomerically pure **11**: mp 138 °C; IR (Nujol) 2253, 1742 cm^{-1}; HRMS (FAB) m/z = 520.3318 (M$^+$ calcd for $C_{29}H_{48}N_2O_4S$ 520.3334); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3H), 1.03 (s, 3H), 1.05 (d, 3H, J = 6.9 Hz), 1.12 (d, 3H, J = 6.9 Hz), 1.49 (s, 3H), 1.00–2.10 (m, 27H), 2.24 (m, 1H, J = 6.9 Hz), 2.58 (d, 1H, J = 13.2 Hz), 3.20–3.38 (m, 2H), 3.36 (d, 1H, 13.2 Hz), 4.95 (dd, 1H, J = 7.5 Hz, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.9, 19.5, 19.9, 20.3, 21.5, 25.0, 26.1, 26.3, 30.5, 31.9, 33.4, 34.1, 39.4, 44.1, 49.2, 49.3, 49.4, 53.3, 57.2, 80.2, 118.9, 168.1. C, 69.97; H, 8.58; N, 4.87; S, 5.46. Anal. Calcd for $C_{29}H_{48}N_2O_4S$: C, 66.88; H, 9.29; N, 5.38; S, 6.16. Found: C, 67.02; H, 9.36; N, 5.47; S, 6.04.

(2*R*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2-isopropyl-4-pentenoate (12). The general procedure was followed for the alkylation of 506 mg (1 mmol) of **3** with 1.21 g (10 mmol) of CH_2CHCH_2Br. Purification of the crude product by flash chromatography and recrystallization afforded 345 mg (63% yield) of diastereomerically pure **12**: mp 162 °C; IR (Nujol) 2249, 1735 cm^{-1}; HRMS (FAB) m/z = 546.3474 (M$^+$ calcd for $C_{31}H_{50}N_2O_4S$ 546.3491); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 1.02 (s, 3H), 1.09 (d, 3H, J = 6.6 Hz), 1.14 (d, 3H, J = 6.6 Hz), 1.00–2.05 (m, 27H), 2.23 (m, 1H, J = 6.6 Hz), 2.50 (dd, 1H, J = 13.5 Hz, J = 6.9 Hz), 2.56 (d, 1H, J = 13.2 Hz), 2.61 (dd, 1H, J = 13.5 Hz, J = 6.9 Hz), 3.22–3.34 (m, 2H), 3.38 (d, 1H, 13.2 Hz), 4.89 (dd, 1H, J = 7.8 Hz, J = 2.7 Hz), 5.12–5.26 (m, 2H), 5.72–5.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 19.7, 19.9, 21.4, 25.2, 26.2, 26.4, 27.0, 30.6, 31.9, 33.6, 34.3, 39.7, 40.4, 44.3, 49.3, 49.5, 53.3, 54.5, 57.2, 81.2, 118.0, 120.8, 131.0, 167.6. Anal. Calcd for $C_{31}H_{50}N_2O_4S$: C, 68.09; H, 9.22; N, 5.12; S, 5.86. Found: C, 68.16; H, 9.31; N, 5.04; S, 5.93.

(2*R*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Benzyl-2-cyano-3-methylbutanoate (13). The general procedure was followed for the alkylation of 506 mg (1 mmol) of **3** with 2.18 g (10 mmol) of $C_6H_5CH_2I$. Purification of the crude product by flash chromatography and recrystallization afforded 475 mg (80% yield) of diastereomerically pure **13**: mp 212 °C; IR (Nujol) 2242, 1735 cm^{-1}; HRMS (FAB) m/z = 596.3665 (M$^+$ calcd for $C_{35}H_{52}N_2O_4S$ 596.3647); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.20 (s, 3H), 0.68 (s, 3H), 1.19 (d, 3H, J = 6.9 Hz), 1.21 (d, 3H, J = 6.9 Hz), 0.98–2.00 (m, 27H), 2.35 (m, 1H, J = 6.9 Hz), 2.42 (d, 1H, J = 13.2 Hz), 2.98 (d, 1H, J = 13.2 Hz), 3.17 (d, 1H, 13.2 Hz), 3.20–3.36 (m, 2H), 3.24 (d, 1H, J = 13.2 Hz), 4.69 (dd, 1H, J = 7.5 Hz, J = 3.0 Hz), 7.20–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7, 19.2, 19.9, 20.3, 25.2, 26.2, 26.4, 26.9, 30.4, 31.8, 33.6, 36.0, 39.2, 42.0, 44.2, 48.9, 49.2, 53.0, 56.7, 57.1, 81.1, 118.2, 127.7, 128.4, 130.5, 134.4, 167.4. Anal. Calcd for $C_{35}H_{52}N_2O_4S$: C, 70.43; H, 8.78; N, 4.70; S, 5.37. Found: C, 70.57; H, 8.69; N, 4.82; S, 5.41.

(2*R*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2-methyl-3-phenylpropanoate (14). The general procedure was followed for the alkylation of 554 mg (1 mmol) of **4** with 1.42 g (10 mmol) of CH_3I. Purification of the crude product by flash chromatography and recrystallization afforded 295 mg (52% yield) of diastereomerically pure **14** whose physical and spectroscopic data have been previously described.[6]

(2*R*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Benzyl-2-cyano-4-pentenoate (15). The general procedure was followed for the alkylation of 554 mg (1 mmol) of **4** with 1.21 g (10 mmol) of CH_2CHCH_2Br. Purification of the crude product by flash chromatography afforded 385 mg (65% yield) of compound **15** as a mixture of diastereoisomers (dr 92/8) whose physical and spectroscopic data have been previously described.[6]

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2-phenylpropanoate (16). The general procedure was followed for the alkylation of 540 mg (1 mmol) of **5** with 1.42 g (10 mmol) of CH_3I. Purification of the crude product by flash chromatography and recrystallization afforded 355 mg (64% yield) of diastereomerically pure **16**: mp 141 °C; IR (Nujol) 2253, 1742 cm^{-1}; HRMS (FAB) m/z = 554.3167 (M$^+$ calcd for $C_{32}H_{46}N_2O_4S$ 554.3178); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H), 0.97 (s, 3H), 1.97 (s, 3H), 1.00–2.08 (m, 27H), 2.60 (d, 1H, J = 13.2 Hz), 3.10–3.30 (m, 2H), 3.34 (d, 1H, 13.2 Hz), 5.01 (dd, 1H, J = 7.8 Hz, J = 2.7 Hz), 7.30–7.40 (m, 3H), 7.52–7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9, 20.3, 25.0, 25.3, 26.2, 26.3, 26.9, 30.5, 32.1, 33.3, 39.4, 44.3, 49.3, 49.7, 53.6, 57.4, 66.5, 81.2, 119.9, 125.7, 126.4, 128.7, 128.9, 167.0. Anal. Calcd for $C_{32}H_{46}N_2O_4S$: C, 69.28; H, 8.36; N, 5.05; S, 5.78. Found: C, 69.42; H, 8.43; N, 4.93; S, 5.62.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2-phenyl-4-pentenoate (17). The general procedure was followed for the alkylation of 540 mg (1 mmol) of **5** with 1.21 g (10 mmol) of CH_2CHCH_2Br. Purification of the crude product by flash chromatography and recrystallization afforded 480 mg (83% yield) of diastereomerically pure **17**: mp 158 °C; IR (Nujol) 2245, 1740 cm^{-1}; HRMS (FAB) m/z = 580.3296 (M$^+$ calcd for $C_{34}H_{48}N_2O_4S$ 580.3334); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H), 1.02 (s, 3H), 0.80–2.10 (m, 27H), 2.58 (d, 1H, J = 13.2 Hz), 2.89 (dd, 1H, J = 13.5 Hz, J = 6.6 Hz), 3.03 (dd, 1H, J = 13.5 Hz, J = 8.1 Hz), 3.08–3.20 (m, 2H), 3.36 (d, 1H, J = 13.2 Hz), 4.99 (dd, 1H, J = 7.8 Hz, J = 3.0 Hz), 5.20–5.36 (m, 2H), 5.80–5.96 (m, 1H), 7.26–7.40 (m, 3H), 7.56–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9, 20.4, 25.0, 26.2, 26.3, 26.9, 30.5, 32.1, 33.3, 39.6, 44.1, 44.4, 49.3, 49.6, 53.2, 53.4, 57.4, 80.7, 118.7, 121.6, 126.7, 128.7, 128.9, 130.5, 134.5, 166.0. Anal. Calcd for $C_{34}H_{48}N_2O_4S$: C, 70.31; H, 8.33; N, 4.82; S, 5.52. Found: C, 70.48; H, 8.42; N, 4.76; S, 5.58.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2,3-diphenylpropanoate (18). The general procedure was followed for the alkylation of 540 mg (1 mmol) of **5** with 2.18 g (10 mmol) of $C_6H_5CH_2I$. Purification of the crude product by flash chromatography and recrystallization afforded 505 mg (80% yield) of diastereomerically pure **18**: mp 221 °C; IR (Nujol) 2235, 1746 cm^{-1}; HRMS (FAB) m/z = 630.3480 (M$^+$ calcd for $C_{38}H_{50}N_2O_4S$ 630.3491); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.44 (s, 3H), 0.73 (s, 3H), 0.80–2.00 (m, 27H), 2.47 (d, 1H, J = 13.2 Hz), 3.02–3.18 (m, 2H), 3.27 (d, 1H, J = 13.2 Hz), 3.41 (d, 1H, 13.2 Hz), 3.54 (d, 1H, J = 13.2 Hz), 4.87 (dd, 1H, J = 7.8 Hz, J = 3.3 Hz), 7.26–7.44 (m, 8H), 7.68–7.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 20.2, 25.0, 26.1, 26.2, 26.9, 30.4, 31.9, 33.3, 38.9, 44.3, 45.8, 49.1, 49.4, 53.3, 55.0, 57.3, 81.4, 119.1, 126.8, 128.0, 128.4, 128.8, 128.9, 130.7, 135.2, 165.7. Anal. Calcd for $C_{38}H_{50}N_2O_4S$: C, 72.35; H, 7.99; N, 4.44; S, 5.08. Found: C, 72.52; H, 8.12; N, 4.35; S, 4.98.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-Cyano-2-phenylbutanoate (19). The general procedure was followed for the alkylation of 540 mg (1 mmol) of **5** with 1.56 g (10 mmol) of CH_3CH_2I. Purification of the crude product by flash chromatography and recrystallization afforded 480 mg (85% yield) of diastereomerically pure **19**: mp 163 °C; IR (Nujol) 2238, 1736 cm^{-1}; HRMS (FAB) m/z = 568.3379 (M$^+$ calcd for $C_{33}H_{48}N_2O_4S$ 568.3334); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3H), 1.02 (s, 3H), 1.13 (t, 3H, J = 7.5 Hz), 1.00–2.20 (m, 29H), 2.59 (d, 1H, J = 13.2 Hz), 3.05–3.16 (m, 2H), 3.36 (d, 1H, 13.2 Hz), 5.00 (dd, 1H, J = 7.5 Hz, J = 2.7 Hz), 7.28–7.38 (m, 3H), 7.55–7.60

(m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.1, 19.9, 20.4, 25.0, 26.2, 26.3, 26.9, 30.5, 32.0, 33.3, 33.7, 39.7, 44.4, 49.3, 49.6, 53.4, 54.5, 57.3, 81.5, 118.9, 126.7, 128.6, 128.8, 134.9, 166.5. Anal. Calcd for $C_{33}H_{48}N_2O_4S$: C, 69.68; H, 8.51; N, 4.92; S, 5.64. Found: C, 69.62; H, 8.41; N, 4.99; S, 5.56.

Preparation of Silyl Enol Ether Z-O. To a dry THF solution (10 mL) of lithium diisopropylamide (0.22 mmol), under argon at −78 °C, was added a solution of 2-cyano ester **4** (111 mg, 0.2 mmol) in dry THF (5 mL). The reaction mixture was stirred at −78 °C for 1 h and after a solution of ^{t}butyldimethylsilyl chloride (45 mg, 0.3 mmol) in dry THF (5 mL) was added by syringe. The reaction mixture was allowed to warm to room temperature and stirring was continued for 1 h. The solvent was removed in vacuo and the residue extracted with ether. Filtration under argon and subsequent concentration in vacuo afforded the corresponding **Z-O** which was subjected to NMR analysis: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 6H), 0.92 (s, 9H), 1.02–2.20 (m, 27H), 1.46 (s, 3H), 1.50 (s, 3H), 2.43 (d, 1H, J = 13 Hz), 3.86–4.00 (m, 3H), 4.29–4.36 (m, 2H), 5.50 (dd, 1H, J = 6.0 Hz, J = 2.3 Hz), 7.20–7.40 (m, 5H).

Preparation of Silyl Enol Ether E-O. To a dry THF solution (10 mL) of lithium diisopropylamide (0.22 mmol), under argon at −78 °C, was added a solution of 2-cyano ester **5** (108 mg, 0.2 mmol) in dry THF (5 mL). The reaction mixture was stirred at −78 °C for 1 h and after a solution of ^{t}butyldimethylsilyl chloride (45 mg, 0.3 mmol) in dry THF (5 mL) was added by syringe. The reaction mixture was allowed to warm to room temperature and stirring was continued for 1 h. The solvent was removed in vacuo and the residue extracted with ether. Filtration under argon and subsequent concentration in vacuo afforded the corresponding **E-O** which was subjected to NMR analysis: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 6H), 0.85 (s, 3H), 0.88 (s, 9H), 1.03 (s, 3H), 0.80–2.10 (m, 27H), 2.60 (d, 1H, J = 13.8 Hz), 3.00–3.12 (m, 2H), 3.22 (d, 1H, J = 13.8 Hz), 5.20 (dd, 1H, J = 7.8 Hz, J = 3.3 Hz), 7.42–7.50 (m, 2H), 7.56–7.64 (m, 1H), 8.04–8.12 (m, 2H).

General Method for Nitrile Hydrogenation. A solution of the corresponding cyano ester **6–17** or **19** (1 mmol) in 1% ammonia in ethanol (25 mL) was hydrogenated with 5% rhodium on alumina (400 mg) at 35 °C and atmospheric pressure. The reaction was followed by TLC (kieselgel Merck 60 F_{254}), and when the reaction was finished (24 h), the catalyst was removed by filtration and the filtrate was evaporated to dryness to afford the corresponding β-amino ester **20–32** as a single diastereomer in nearly quantitative yield. Purification of the residue by flash chromatography (silica gel, 60, eluent: hexane/2-propanol 8/2) afforded diastereomerically pure samples of compounds **20–32**.

***(2S)*-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2-methylpentanoate (20).** Derivative **6** (518 mg, 1 mmol) was hydrogenated according to the general procedure to afford 471 mg (90% yield) of β-amino ester **20**: mp 116 °C; IR (Nujol) 3395, 3327, 1723 cm^{-1}; HRMS (FAB) m/z = 525.3729 (MH^+ calcd for $C_{29}H_{53}N_2O_4S$ 525.3722); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, J = 6.6 Hz), 0.85 (s, 3H), 0.96 (s, 3H), 1.10 (s, 3H), 1.00–2.05 (m, 33H), 2.55 (d, 1H, J = 13.2 Hz), 2.59 (d, 1H, J = 13.2 Hz), 2.87 (d, 1H, J = 13.2 Hz), 3.22 (d, 1H, J = 13.2 Hz), 3.40–3.65 (m, 2H), 4.79 (dd, 1H, J = 7.8 Hz, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 17.7, 18.9, 19.9, 20.4, 25.1, 26.3, 26.4, 27.0, 30.7, 32.1, 33.5, 39.1, 40.1, 44.3, 48.7, 49.1, 49.4, 51.3, 53.8, 57.3, 78.7, 174.9. Anal. Calcd for $C_{29}H_{52}N_2O_4S$: C, 66.37; H, 9.99; N, 5.34; S, 6.11. Found: C, 66.52; H, 10.09; N, 5.24; S, 6.24.

***(2S)*-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2-methyl-3-phenylpropanoate (21).** Derivative **7** (568 mg, 1 mmol) was hydrogenated according to the general procedure to afford 496 mg (87% yield) of β-amino ester **21**: oil; IR (Nujol) 3405, 3325, 1714 cm^{-1}; HRMS (FAB) m/z = 573.3257 (MH^+ calcd for $C_{33}H_{53}N_2O_4S$ 573.3722); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 0.93 (s, 3H), 1.19 (s, 3H), 1.00–2.00 (m, 27H), 2.63 (m, 2H), 2.87 (m, 2H), 3.02 (d, 1H, 13.5 Hz), 3.12–3.30 (m, 2H), 3.25 (d, 1H, J = 13.5 Hz), 3.36 (brs, 2H), 4.91 (dd, 1H, J = 7.8 Hz, J = 3.0 Hz), 7.05–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.0, 20.4, 20.7, 25.1, 26.2, 26.3, 27.0, 30.8, 32.1, 33.4, 39.9, 42.2, 44.3, 47.5, 47.7, 49.1, 49.5, 54.1, 57.4, 79.3, 126.6, 128.2, 130.3, 136.4, 174.6.

***(2R)*-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2-methylbutanoate (22).** Derivative **8** (506 mg, 1 mmol) was hydrogenated according to the general procedure to afford 472 mg (93% yield) of β-amino ester **22**: mp 131 °C; IR (Nujol) 3394, 3330, 1721 cm^{-1}; HRMS (FAB) m/z = 511.3547 (MH^+ calcd for $C_{28}H_{51}N_2O_4S$ 511.3565); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, 3H, J = 8.4 Hz), 0.79 (s, 3H), 0.93 (s, 3H), 1.10 (s, 3H), 1.00–2.00 (m, 29H), 2.36 (brs, 2H), 2.54 (d, 1H, J = 13.2 Hz), 2.61 (d, 1H, J = 13.2 Hz), 2.86 (d, 1H, J = 13.2 Hz), 3.15 (d, 1H, J = 13.2 Hz), 3.08–3.28 (m, 2H), 4.80 (dd, 1H, J = 7.5 Hz, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.5, 19.0, 19.9, 20.3, 25.0, 26.3, 26.9, 29.5, 30.6, 32.0, 33.4, 40.0, 44.2, 48.1, 49.0, 49.3, 49.6, 53.8, 57.2, 78.4, 175.1. Anal. Calcd for $C_{28}H_{50}N_2O_4S$: C, 65.84; H, 9.87; N, 5.48; S, 6.28. Found: C, 65.91; H, 9.79; N, 5.56; S, 6.34.

***(2S)*-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2-ethylpentanoate (23).** Derivative **9** (532 mg, 1 mmol) was hydrogenated according to the general procedure to afford 500 mg (93% yield) of β-amino ester **23**: oil; IR (Nujol) 3403, 3317, 1724 cm^{-1}; HRMS (FAB) m/z = 539.3348 (MH^+ calcd for $C_{30}H_{55}N_2O_4S$ 539.3878); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, 3H, J = 7.5 Hz), 0.78 (s, 3H), 0.81 (t, 3H, J = 7.2 Hz), 0.91 (s, 3H), 1.00–2.00 (m, 33H), 2.55 (d, 1H, J = 13.2 Hz), 2.74–2.84 (m, 2H), 3.16 (d, 1H, 13.2 Hz), 3.10–3.36 (m, 2H), 3.30 (brs, 2H), 4.75 (dd, 1H, J = 7.8 Hz, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.8, 14.3, 17.0, 19.8, 20.3, 24.9, 26.2, 26.3, 26.8, 30.6, 31.9, 33.3, 34.5, 40.0, 44.1, 45.0, 48.9, 49.3, 50.6, 53.8, 57.2, 78.9, 174.6.

***(2S)*-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2-benzylbutanoate (24).** Derivative **10** (582 mg, 1 mmol) was hydrogenated according to the general procedure to afford 486 mg (83% yield) of β-amino ester **24**: oil; IR (Nujol) 3393, 3322, 1719 cm^{-1}; HRMS (FAB) m/z = 587.3865 (MH^+ calcd for $C_{34}H_{55}N_2O_4S$ 587.3878); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (s, 3H), 0.82 (s, 3H), 0.97 (t, 3H, J = 7.5 Hz), 1.00–2.05 (m, 29H), 2.60 (d, 1H, J = 13.8 Hz), 2.86 (s, 2H), 2.96 (d, 1H, J = 13.8 Hz), 3.08 (d, 1H, J = 13.8 Hz), 3.10–3.32 (m, 2H), 3.22 (d, 1H, 13.8 Hz), 4.89 (dd, 1H, J = 7.8 Hz, J = 2.7 Hz), 5.43 (brs, 2H), 7.10–7.20 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.8, 19.7, 20.3, 24.9, 26.0, 26.2, 26.3, 26.8, 26.2, 30.7, 31.9, 33.2, 39.8, 39.9, 40.6, 44.1, 47.7, 49.0, 49.4, 54.0, 57.4, 80.3, 127.2, 128.5, 130.2, 134.7, 172.8. Anal. Calcd for $C_{34}H_{54}N_2O_4S$: C, 69.59; H, 9.27; N, 4.77; S, 5.46. Found: C, 69.36; H, 9.09; N, 4.58; S, 5.59.

***(2R)*-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2,3-dimethylbutanoate (25).** Derivative **11** (520 mg, 1 mmol) was hydrogenated according to the general procedure to afford 475 mg (91% yield) of β-amino ester **25**: oil; IR (Nujol) 3400, 3326, 1723 cm^{-1}; HRMS (FAB) m/z = 525.3719 (MH^+ calcd for $C_{29}H_{53}N_2O_4S$ 525.3722); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 3H), 0.86 (d, 6H, J = 6.6 Hz), 0.93 (s, 3H), 1.27 (s, 3H), 1.00–2.00 (m, 27H), 2.04 (m, 1H, J = 6.6 Hz), 2.57 (d, 1H, J = 13.5 Hz), 2.96 (d, 1H, J = 13.2 Hz), 3.12 (d, 1H, J = 13.5 Hz), 3.10–3.30 (m, 2H), 3.25 (d, 1H, 13.2 Hz), 4.96 (dd, 1H, J = 7.8, J = 2.7 Hz), 8.00 (brs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.8, 17.6, 19.8, 20.2, 25.0, 26.1, 26.3, 26.8, 31.0, 32.0, 33.3, 33.5, 39.0, 43.0, 44.3, 47.4, 49.0, 49.7, 54.5, 57.5, 78.9, 175.0.

***(2R)*-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2-isopropylpentenoate (26).** Derivative **12** (546 mg, 1 mmol) was hydrogenated according to the general procedure to afford 480 mg (87% yield) of β-amino ester **26**: oil; IR (Nujol) 3398, 3325, 1731 cm^{-1}; HRMS (FAB) m/z = 553.4014 (MH^+ calcd for $C_{31}H_{57}N_2O_4S$ 553.4035); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (s, 3H), 0.89 (t, 3H, J = 6.0 Hz), 0.91 (d, 6H, J = 6.6 Hz), 0.97 (s, 3H), 1.00–2.00 (m, 31H), 2.04 (m, 1H, J = 6.6 Hz), 2.61 (d, 1H, J = 13.5 Hz), 2.82 (d, 1H, J = 13.2 Hz), 3.02 (d, 1H, J = 13.2 Hz), 3.10–3.30 (m, 2H), 3.18 (d, 1H, 13.5 Hz), 3.40 (brs, 2H), 4.87 (dd, 1H, J = 7.8 Hz, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.8, 17.5, 17.8, 18.3, 20.0, 20.4, 25.0, 26.3, 26.9, 30.9, 31.4, 32.1, 33.3, 33.6, 40.0, 43.8, 44.3, 49.0, 49.5, 52.8, 54.1, 57.3, 79.1, 174.4.

***(2R)*-(*1S,2R,4R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2-benzyl-3-methylbutanoate (27).** Derivative **13** (596 mg, 1 mmol) was hydrogenated according to the general procedure to afford 500 mg (84% yield) of β-amino ester **27**: oil; IR (Nujol) 3400, 3333, 1734 cm^{-1}; HRMS (FAB) m/z = 601.4063 (MH^+ calcd for $C_{35}H_{57}N_2O_4S$ 601.4038); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.72 (s, 3H), 0.79 (s, 3H), 1.12 (d, 3H, J = 6.9 Hz), 1.15 (d, 3H, J = 6.9 Hz), 0.90–2.00 (m, 27H), 2.19 (m, 1H, J = 6.9 Hz), 2.66 (d, 1H, J = 13.8 Hz), 2.93 (d, 1H, J = 14.1 Hz),

3.06–3.30 (m, 5H), 3.37 (d, 1H, J = 14.1 Hz), 4.88 (dd, 1H, J = 7.5 Hz, J = 2.7 Hz), 7.20 (s, 5H), 7.8 (brs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 19.2, 19.7, 20.2, 25.0, 26.1, 26.2, 26.8, 31.2, 31.9, 33.0, 33.3, 39.8, 40.3, 40.5, 44.1, 49.1, 49.8, 52.5, 54.9, 57.4, 80.9, 127.3, 128.7, 130.4, 135.2, 172.9.

(2*R*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2-methyl-3-phenylpropanoate (28). Derivative **14** (568 mg, 1 mmol) was hydrogenated according to the general procedure to afford 530 mg (93% yield) of β-amino ester **28** whose physical and spectroscopic data have been previously described.[6]

(2*R*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-2-benzylpentanoate (29). Derivative **15** (594 mg, 1 mmol) was hydrogenated according to the general procedure to afford 544 mg (91% yield) of β-amino ester **29** whose physical and spectroscopic data have been previously described.[6]

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-(Aminomethyl)-3-phenylpropanoate (30). Derivative **16** (554 mg, 1 mmol) was hydrogenated according to the general procedure to afford 450 mg (81% yield) of β-amino ester **30**: oil; IR (Nujol) 3402, 3331, 1733 cm^{-1}; HRMS (FAB) m/z = 559.3578 (MH^+ calcd for $C_{32}H_{51}N_2O_4S$ 559.3565); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.26 (s, 3H), 0.67 (s, 3H), 0.80–1.80 (m, 27H), 1.82 (s, 3H), 2.45 (d, 1H, J = 13.2 Hz), 2.95 (d, 1H, J = 13.2 Hz), 3.10–3.26 (m, 2H), 3.16 (d, 1H, J = 13.2 Hz), 3.44 (d, 1H, 13.2 Hz), 4.88 (dd, 1H, J = 7.5 Hz, J = 2.7 Hz), 6.05 (brs, 2H), 7.06–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 19.8, 20.1, 24.9, 26.2, 26.7, 26.9, 30.5, 31.9, 33.2, 38.5, 43.9, 47.1, 48.4, 48.8, 49.2, 53.7, 57.3, 79.2, 125.9, 127.9, 128.9, 138.0, 173.0.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 3-(Aminomethyl)-3-phenylpentanoate (31). Derivative **17** (580 mg, 1 mmol) was hydrogenated according to the general procedure to afford 380 mg (65% yield) of β-amino ester **31**: oil; IR (Nujol) 3394, 3325, 1715 cm^{-1}; HRMS (FAB) m/z = 587.3891 (MH^+ calcd for $C_{34}H_{55}N_2O_4S$ 587.3878); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 (s, 3H), 0.88 (t, 3H, J = 7.2 Hz), 1.77 (s, 3H), 0.88–2.00 (m, 33H), 2.54 (d, 1H, J = 13.5 Hz), 2.94 (brs, 2H), 3.05 (d, 1H, J = 13.5 Hz), 3.02–3.32 (m, 2H), 4.83 (dd, 1H, J = 7.8 Hz, J = 3.0 Hz), 7.10–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 17.5, 19.4, 20.2, 24.9, 26.2, 26.8, 30.6, 31.9, 33.3, 35.8, 39.8, 44.1, 47.1, 48.9, 49.3, 53.7, 56.4, 57.2, 79.2, 126.5, 127.1, 128.2, 140.8, 173.5.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 3-(Aminomethyl)-3-phenylbutanoate (32). Derivative **19** (568 mg, 1 mmol) was hydrogenated according to the general procedure to afford 455 mg (80% yield) of β-amino ester **32**: oil; IR (Nujol) 3396, 3318, 1722 cm^{-1}; HRMS (FAB) m/z = 573.3743 (MH^+ calcd for $C_{33}H_{53}N_2O_4S$ 573.3722); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.45 (s, 3H), 0.74 (s, 3H), 0.96 (t, 3H, J = 7.5 Hz), 1.00–2.25 (m, 29H), 2.52 (d, 1H, J = 13.5 Hz), 3.10 (d, 1H, 13.5 Hz), 3.15–3.20 (m, 4H), 3.68 (brs, 2H), 4.83 (dd, 1H, J = 7.5 Hz, J = 3.0 Hz), 7.20–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.9, 19.1, 20.3, 25.1, 26.4, 26.9, 30.6, 32.0, 33.4, 39.5, 44.1, 45.1, 48.9, 49.3, 53.8, 55.2, 57.3, 79.5, 126.8, 127.2, 128.7, 139.8, 173.1.

General Procedure for β-Amino Acid Cyclization. To a stirred solution of methylmagnesium bromide (0.5 mL of 3.0 M solution in ether, 1.5 mmol) in ether (25 mL) was added dropwise compound **20–32** (0.5 mmol) in ether (5 mL) and the mixture was stirred for 3 h at room temperature. When the reaction was finished, aqueous 10% ammonium chloride (25 mL) was added and the mixture was stirred until the two layers became clear. The aqueous layer was separated and extracted with ether. The combined ether solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the corresponding β-lactam **33–45** as a crude oil, which was chromatographed on a silica gel column (eluent ether/hexane 3/1) to afford enantiomerically pure samples of 3,3-dialkylsubstituted β-lactam **33–45**.

(3*S*)-3-Methyl-3-propyl-2-azetidinone (33). Derivative **20** (262 mg, 0.5 mmol) was cyclized according to the general procedure to afford 60.8 mg (96% yield) of β-lactam **33**: oil; $[\alpha]_D$ = +21.43° (c = 1.40 in $CHCl_3$), IR (Nujol) 3263, 1750 cm^{-1}; HRMS (EI) m/z = 128.1067 (MH^+ calcd for $C_7H_{14}NO$ 128.1075); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, J = 7.2 Hz), 1.23 (s, 3H), 1.20–1.54 (m, 4H), 2.95 (d, 1H, J = 5.1 Hz), 3.10 (d, 1H, J = 5.1 Hz), 6.30 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 17.9, 19.3, 36.7, 48.6, 56.2, 175.2.

(3*S*)-3-Benzyl-3-methyl-2-azetidinone (34). Derivative **21** (286 mg, 0.5 mmol) was cyclized according to the general procedure to afford 78 mg (90% yield) of β-lactam **34**: mp 98 °C; $[\alpha]_D$ = +43.3° (c = 0.30 in $CHCl_3$), IR (Nujol) 3246, 1767 cm^{-1}; HRMS (EI) m/z = 176.1071 (MH^+ calcd for $C_{11}H_{14}NO$ 176.1075); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 3H), 2.74 (d, 1H, J = 13.8 Hz), 2.96 (d, 1H, J = 5.4 Hz), 3.02 (d, 1H, J = 13.8 Hz), 3.20 (d, 1H, J = 5.4 Hz), 5.06 (brs, 1H), 7.16–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.1, 40.5, 47.4, 57.2, 126.6, 128.3, 129.9, 137.0, 174.1. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.57; H, 7.57; N, 8.13.

(3*R*)-3-Ethyl-3-methyl-2-azetidinone (35). Derivative **22** (255 mg, 0.5 mmol) was cyclized according to the general procedure to afford 54 mg (96% yield) of β-lactam **35**: oil; $[\alpha]_D$ = −24.0° (c = 0.25 in $CHCl_3$), IR (Nujol) 3259, 1749 cm^{-1}; HRMS (EI) m/z = 114.0925 (MH^+ calcd for $C_6H_{12}NO$ 114.0918); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H, J = 7.5 Hz), 1.29 (s, 3H), 1.56–1.72 (m, 2H), 2.99 (d, 1H, J = 5.4 Hz), 3.15 (d, 1H, J = 5.4 Hz), 5.74 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.9, 19.1, 27.4, 30.3, 48.0, 174.7.

(3*S*)-3-Ethyl-3-propyl-2-azetidinone (36). Derivative **23** (269 mg, 0.5 mmol) was cyclized according to the general procedure to afford 66 mg (95% yield) of β-lactam **36**: oil; $[\alpha]_D$ = −6.75° (c = 0.80 in $CHCl_3$), IR (Nujol) 3250, 1747 cm^{-1}; HRMS (EI) m/z = 142.1227 (MH^+ calcd for $C_8H_{16}NO$ 142.1231); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 6.9 Hz), 0.92 (t, 3H, J = 7.5 Hz), 1.20–1.60 (m, 4H), 1.63 (c, 2H, J = 7.2 Hz), 3.04 (s, 2H), 6.08 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.7, 14.4, 17.7, 25.5, 34.7, 45.6, 60.9, 174.5.

(3*S*)-3-Benzyl-3-ethyl-2-azetidinone (37). Derivative **24** (293 mg, 0.5 mmol) was cyclized according to the general procedure to afford 85 mg (91% yield) of β-lactam **37**: oil; $[\alpha]_D$ = +55.49° (c = 0.70 in $CHCl_3$), IR (Nujol) 3154, 1748 cm^{-1}; HRMS (EI) m/z = 189.1158 (M^+ calcd for $C_{12}H_{15}NO$ 189.1152); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, 3H, J = 7.5 Hz), 1.60–1.80 (m, 2H), 2.79 (d, 1H, J = 13.8 Hz), 3.03 (d, 1H, J = 5.7 Hz), 3.04 (d, 1H, J = 13.8 Hz), 3.09 (d, 1H, J = 5.7 Hz), 5.72 (brs, 1H), 7.28–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.8, 26.2, 38.8, 44.1, 61.6, 126.5, 128.2, 129.9, 136.9, 173.4.

(3*R*)-3-Isopropyl-3-methyl-2-azetidinone (38). Derivative **25** (262 mg, 0.5 mmol) was cyclized according to the general procedure to afford 60 mg (96% yield) of β-lactam **38**: mp 83 °C; $[\alpha]_D$ = −61.57° (c = 0.50 in $CHCl_3$), IR (Nujol) 3194, 1737 cm^{-1}; HRMS (EI) m/z = 128.1069 (MH^+ calcd for $C_7H_{14}NO$ 128.1075); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, 3H, J = 6.9 Hz), 0.95 (d, 3H, J = 6.9 Hz), 1.25 (s, 3H), 1.87 (m, 1H, J = 6.9 Hz), 2.91 (d, 1H, J = 5.7 Hz), 3.13 (d, 1H, J = 5.7 Hz), 5.99 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.4, 17.5, 18.1, 31.2, 46.9, 60.4, 174.9. Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.28; H, 10.16; N, 11.09.

(3*R*)-3-Isopropyl-3-propyl-2-azetidinone (39). Derivative **26** (276 mg, 0.5 mmol) was cyclized according to the general procedure to afford 67 mg (87% yield) of β-lactam **39**: oil; $[\alpha]_D$ = −44.55° (c = 0.65 in $CHCl_3$), IR (Nujol) 3255, 1744 cm^{-1}; HRMS (EI) m/z = 156.1382 (MH^+ calcd for $C_9H_{18}NO$ 156.1388); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 7.2 Hz), 0.93 (d, 3H, J = 6.6 Hz), 0.94 (d, 3H, J = 6.6 Hz), 1.32–1.46 (m, 2H), 1.57 (t, 2H, J = 7.5 Hz), 1.91 (m, 1H, J = 6.6 Hz), 2.96 (d, 1H, J = 5.7 Hz), 3.06 (d, 1H, J = 5.7 Hz), 5.97 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 17.4, 17.6, 18.1, 29.9, 32.6, 43.4, 64.6, 174.0.

(3*R*)-3-Benzyl-3-isopropyl-2-azetidinone (40). Derivative **27** (300 mg, 0.5 mmol) was cyclized according to the general procedure to afford 95 mg (94% yield) of β-lactam **40**: mp 92 °C; $[\alpha]_D$ = +36.5° (c = 1.00 in $CHCl_3$), IR (Nujol) 3213, 1739 cm^{-1}; HRMS (EI) m/z = 204.1393 (MH^+ calcd for $C_{13}H_{18}NO$ 204.1388); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (d, 3H, J = 6.6 Hz), 1.06 (d, 3H, J = 6.6 Hz), 2.00 (m, 1H, J = 6.6 Hz), 2.78 (d, 1H, J = 13.8 Hz), 2.90 (d, 1H, J = 5.7 Hz), 3.01 (d, 1H, J = 5.7 Hz), 3.02 (d, 1H, J = 13.8 Hz), 5.62 (brs, 1H), 7.18–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7, 18.3, 30.6, 36.0, 42.1, 65.3, 126.4, 128.1, 130.2, 136.9, 173.0. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.96; H, 8.35; N, 6.98.

(3*R*)-3-Benzyl-3-methyl-2-azetidinone (41). Derivative **28** (286 mg, 0.5 mmol) was cyclized according to the general procedure to afford 77 mg (89% yield) of β-lactam **41** whose physical and spectroscopic data have been previously described.[6]

(3R)-3-Benzyl-3-propyl-2-azetidinone (42). Derivative **29** (300 mg, 0.5 mmol) was cyclized according to the general procedure to afford 87 mg (86% yield) of β-lactam **42** whose physical and spectroscopic data have been previously described.[6]

(3S)-3-Methyl-3-phenyl-2-azetidinone (43). Derivative **30** (279 mg, 0.5 mmol) was cyclized according to the general procedure to afford 74 mg (92% yield) of β-lactam **43**: oil; $[\alpha]_D = -40.75°$ ($c = 0.80$ in $CHCl_3$), IR (Nujol) 3240, 1740 cm^{-1}; HRMS (EI) m/z = 162.0925 (MH^+ calcd for $C_{10}H_{12}NO$ 162.0918); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.67 (s, 3H), 3.41 (d, 1H, $J = 5.8$ Hz), 3.55 (d, 1H, $J = 5.8$ Hz), 6.26 (brs, 1H), 7.20–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.4, 51.1, 60.0, 125.8, 127.0, 128.6, 140.7, 172.9.

(3S)-3-Phenyl-3-propyl-2-azetidinone (44). Derivative **31** (293 mg, 0.5 mmol) was cyclized according to the general procedure to afford 88 mg (94% yield) of β-lactam **44**: mp 66 °C; $[\alpha]_D = -44.78°$ ($c = 0.45$ in $CHCl_3$), IR (Nujol) 3200, 1740 cm^{-1}; HRMS (EI) m/z = 189.1149 (M^+ calcd for $C_{12}H_{15}NO$ 189.1153); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, $J = 7.2$ Hz), 1.18–1.48 (m, 2H), 1.88–1.98 (m, 2H), 3.47 (d, 1H, $J = 5.4$ Hz), 3.56 (d, 1H, $J = 5.4$ Hz), 5.99 (brs, 1H), 7.18–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 18.2, 39.8, 48.3, 64.5, 126.5, 126.9, 128.4, 140.0, 172.3. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.97; H, 7.92; N, 7.24.

(3S)-3-Ethyl-3-phenyl-2-azetidinone (45). Derivative **34** (286 mg, 0.5 mmol) was cyclized according to the general procedure to afford 80 mg (92% yield) of β-lactam **45**: oil; $[\alpha]_D = -50.50°$ ($c = 0.30$ in $CHCl_3$), IR (Nujol) 3207, 1737 cm^{-1}; HRMS (EI) m/z = 176.1069 (MH^+ calcd for $C_{11}H_{14}NO$ 176.1075); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, 3H, $J = 7.5$ Hz), 1.99 (c, 2H, $J = 7.5$ Hz), 3.46 (d, 1H, $J = 5.4$ Hz), 3.54 (d, 1H, $J = 5.4$ Hz), 5.07 (brs, 1H), 7.20–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.2, 30.5, 47.8, 64.9, 126.5, 126.9, 128.4, 139.8, 172.3.

Acknowledgment. This work was supported by the Dirección General de Investigación Científica y Técnica, project no. PB91-0696.

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra for compounds **15**, **21**, **23**, **25–27**, **30–33**, **35–37**, **39**, and **42**, **43**, and **45** (34 pages). This material is contained in 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.