(26); exact mass calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2156.

Cyclization of Adduct 23 to 5. A suspension of 1 g (2.28 mmol) of adduct **23** in 90 mL of dry THF was treated with 2.3 mL (4.6 mmol) of *tert*-butyllithium in pentane at -70 °C under dry nitrogen. The reaction mixture was slowly warmed to -30 °C and then stirred at this temperature for 1 h. The mixture was then quenched with saturated ammonium chloride solution and thoroughly extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated, and the residue was chromatographed on silica gel (EtOAc), affording 700 mg (84%) of product homogeneous on TLC. It proved to be identical with **5** (TLC, ^1H NMR).

(±)-*trans*-*N*-Methyl-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)phenyl]-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (28). A solution of 250 mg (0.68 mmol) of **5** in 15 mL of MeOH was treated dropwise with a solution of 465 mg (1.05 mmol) thallium trinitrate trihydrate in 5 mL of MeOH at room temperature. The resulting mixture was stirred for 15 min and then was diluted with 50 mL of CH_2Cl_2 and filtered. The filtrate was concentrated in vacuo to one-third of its volume and diluted with 50 mL of CH_2Cl_2 and then washed with 10% NaOH solution. The organic layer was separated, washed with brine, and dried (Na_2SO_4), and solvent was removed in vacuo to give acetal **25** as a foam, which was used in the next step without purification.

A solution of the acetal **25** obtained above in 25 mL of acetone and 10 mL of 5% HCl solution was stirred for 1 h at 50-60 °C. The reaction mixture was concentrated in vacuo and thoroughly extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried (Na_2SO_4), and evaporated to give aldehyde **26** as a foam in quantitative yield: NMR ($CDCl_3$) δ 9.77 (m, 1 H), 6.75 (d, J = 7.0 Hz, 1 H), 6.65 (s, 1 H), 6.40 (d, J = 7 Hz, 1 H), 6.35 (s, 1 H), 6.10 (s, 2 H), 6.0 (m, 2 H), 4.43 (s, 1 H), 3.70 (br s, 2 H), 3.0 (s, 3 H), 2.95-2.75 (m, 1 H), 1.35 (d, J = 7.0 Hz, 3 H); MS m/e (relative intensity) 381 (20, M^+), 366 (5), 353 (17), 218 (16) 176 (200), 148 (76), 147 (32). The aldehyde **26** was used at once in the following reaction without further purification.

To a vigorously stirred solution of 133 mg (0.84 mmol) of potassium permanganate in 15 mL of water were added tetrabutylammonium bromide (50 mg) and a solution of the above aldehyde **26** in 10 mL of benzene. The mixture was stirred at room temperature until TLC showed complete consumption of the aldehyde (ca 2 h), and it was then diluted with 50 mL of CH_2Cl_2 and treated with 10% sodium bisulfite solution to remove the excess permanganate. The resulting mixture was acidified with 10% HCl solution, the organic layer was separated, and the aqueous layer was throughly extracted with CH_2Cl_2. The combined organic extracts were evaporated in vacuo, and the residue was dissolved in 10% sodium hydroxide solution and washed twice with ether. The aqueous layer was made acidic with concentrated HCl and thoroughly extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to yield 220 mg (81%) of acid **27** as a foam.

Esterification of acid **27** (200 mg) with diazomethane and purification on silica gel (EtOAc) gave 170 mg (82%) of the methyl ester **28**: mp 193-194 °C (EtOAc-hexane) (lit.[4a] mp 190-192 °C); IR ($CHCl_3$) 1730, 1640 cm^{-1}; NMR ($CDCl_3$) δ 6.78 (d, J = 7.8 Hz, 1 H), 6.71 (s, 1 H), 6.42 (d, J = 7.8 Hz, 1 H), 6.35 (s, 1 H), 6.16 (d, J = 1.1 Hz, 1 H), 6.13 (d, J = 1.1 Hz, 1 H), 5.88 (d, J = 1.3 Hz, 1 H), 5.84 (d, J = 1.3 Hz, 1 H), 4.64 (d, J = 1.1 Hz, 1 H), 3.74 (s, 3 H), 3.60 (d, J = 3.9 Hz, 2 H), 3.02 (s, 3 H), 2.90 (q, J = 7.1 Hz, 1 H), 1.42 (d, J = 7.1 Hz, 3 H); MS m/e (relative intensity) 411 (25, M^+), 396 (13), 380 (5), 379 (5), 218 (24), 176 (100), 148 (76), 147 (32). Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.11; N, 3.41. Found: C, 63.90; H, 5.03; N, 3.36.

(±)-Corydalic Acid Methyl Ester (4). The amide **28** (50 mg) was converted to corydalic acid methyl ester (**4**) (32 mg, 66%) with $POCl_3$, and then $NaBH_4$, according to the two-step procedure described by Cushman and Wong:[4a] mp 145-147 °C (lit.[4a] mp 144-147 °C). The synthetic compound proved to be identical with the authentic sample in several solvent systems on silica gel TLC and had NMR and mass spectral data in agreement with those reported.[3,4a]

Acknowledgment. We thank Professor M. Cushman for providing an authentic sample of corydalic acid methyl ester. We are grateful to Dr. J. M. Muchowski for his encouragement and advice and to Lani Russell for preparing the manuscript.

Registry No. (±)-**4**, 88610-31-5; (±)-**5**, 118514-50-4; **8**, 118514-51-5; **9**, 2728-04-3; **10**, 18100-53-3; (±)-**11**, 118514-52-6; **12**, 70946-19-9; **13**, 70946-07-5; **14**, 118514-53-7; **15**, 79809-06-6; **16**, 3811-52-7; (±)-**17**, 118514-54-8; (±)-**23**, 118514-55-9; (±)-**25**, 118537-28-3; (±)-**26**, 118514-56-0; (±)-**27**, 118514-57-1; (±)-**28**, 88610-30-4; 6-bromopiperonal, 15930-53-7.

A Versatile and Stereocontrolled Synthesis of Hydroxyethylene Dipeptide Isosteres

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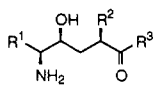
An asymmetric synthesis of the hydroxyethylene dipeptide isostere unit **1** is described. The synthesis provides excellent stereocontrol over all three chiral centers and is amenable to variation of substituents R_1 and R_2. Key intermediate (*S*)-**11** has been obtained by two different asymmetric routes and also by chemical resolution. Bromolactonization of the carboxamide **20** afforded with high 1,3-induction the trans disubstituted γ-lactone **22**, which after conversion to the azido compound **29** was ring opened and reduced to the target compound **6**.

In the course of our work on dipeptide mimics we became interested in the stereoselective synthesis of 2,5-disubstituted 5-amino-4-hydroxypentanoic acid derivatives **1**. Such "hydroxyethylene dipeptide isosters" are of considerable interest as transition state analogues,[1] e.g. in renin inhibitors where they replace the scissile dipeptide unit (Leu-Val) of angiotensinogen, the natural substrate of renin. Syntheses of hydroxyethylene dipeptide mimics were first reported by Szelke[2] and Rich[3] in 1983 and more



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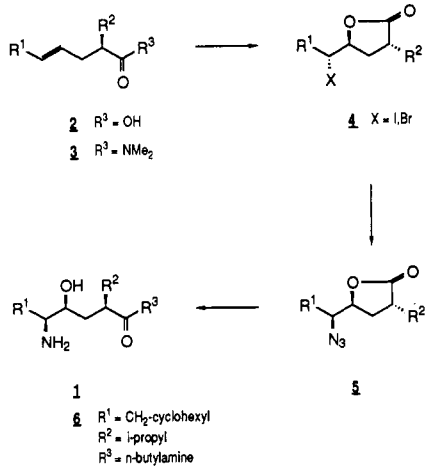
(1) (a) Pauling, L. *Chem. Eng. News* **1946**, *24*, 1375. (b) Wolfenden, R. *Nature* **1969**, *223*, 704.

(2) (a) Szelke, M.; Jones, D. M. European Patent Application EP 45665, 1982; *Chem. Abstr.* **1982**, *97*, 39405. (b) Szelke, M.; Jones, D. M.; Atrash, B.; Hallett, A.; Leckie, B. *Proc. Am. Pept. Symp. (8th)* **1983**, 597.

(3) Holladay, M. W.; Rich, D. H. *Tetrahedron Lett.* **1983**, *24*, 4401.

0022-3263/89/1954-1178$01.50/0

Scheme I



recently by other investigators.[4] In order to control the stereochemistry of the substituents at the C-5 position, all but one[4e] of the previously described routes start with the appropriate enantiomerically pure chiral amino aldehyde, which is readily derived from the corresponding amino acid. While Rich's[4a] and Evans'[4c] syntheses allow stereocontrol at the C-2/C-5 or C-4/C-5 positions, respectively, none of the methods described thus far controls the stereochemistry at all asymmetric centers involved. The following method represents a practical and stereoselective synthesis of **1**, allowing for versatile variations of the 2- and 5-substituents as none of the starting materials is derived from amino acids.

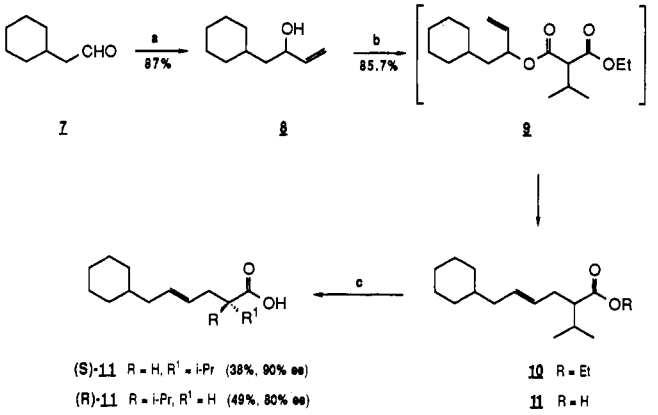
Our synthetic strategy is based on the observation by Yoshida[5] that *N,N*-dimethylamides of α-substituted γ,δ-unsaturated acids **2** are readily iodo lactonized in a thermodynamically controlled reaction to yield the trans disubstituted γ-lactones (Scheme I). Application of this procedure to enantiomerically pure γ,δ-unsaturated carboxamide derivatives **3** was expected to afford the corresponding trans disubstituted γ-lactones **4** with high 1,3 induction, thereby introducing the correct absolute stereochemistry at the C-4 position. S_N2 substitution at C-5 with azide, followed by aminolysis of the lactone ring and reduction of the azide group, would lead to the desired acyclic dipeptide isosteres **1** with complete control of the stereochemistry at C-5. Moreover, the approach summarized in Scheme I offers the opportunity to obtain the target molecule without introduction of any protecting groups.

Herein we report the realization of this protocol, as exemplified by the synthesis of 5-amino-6-cyclohexyl-4-hydroxy-2-isopropylhexanoic acid *n*-butyl amide (**6**), which is a common intermediate for the preparation of potent, reversible renin inhibitors.[6]

Results and Discussion

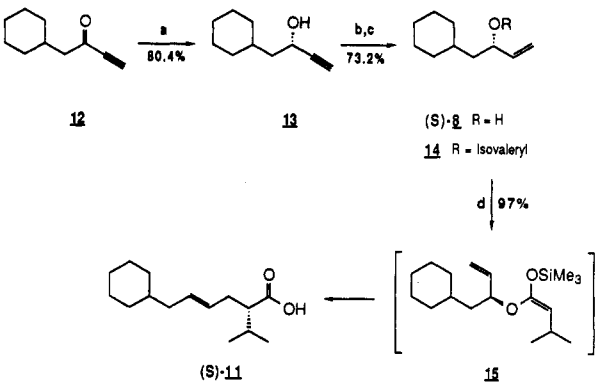
The synthesis of enantiomerically pure (4*E*,2*S*)-6-cyclohexyl-2-isopropyl-4-hexenoic acid (**11**), which served as the starting material for the halo lactonization reaction, is summarized in Scheme II. Addition of vinylmagnesium bromide to cyclohexanecarboxaldehyde **7** in THF afforded the allylic alcohol **8** in 87% yield. Compound **8** was converted with diethyl isopropylmalonate to the mixed malonic ester derivative **9** by $Ti(OEt)_4$ catalysis. Isolation of compound **9** proved unnecessary, since at slightly higher reaction temperatures it underwent directly a [3,3] Carroll type Claisen rearrangement[7] to give the ester **10**. To our surprise, Carroll rearrangement of compound **9** also turned out to be effectively catalyzed by $Ti(OEt)_4$,[8] thereby allowing a one-step conversion of the allylic alcohol **8** to the ester **10**. Direct saponification of the crude product afforded racemic **11** (86% overall yield from **8**), which subsequently was resolved in a two-step crystallization process. After a first crystallization with 1 equiv of quinine, optically active (+)-**11** (80% ee)[9,10] was obtained, leaving the desired (−)-**11** enantiomer in optically highly enriched form in the mother liquor. Recrystallization of the material from

Scheme II[a]



[a] (a) Vinylmagnesium bromide/THF, −78 °C; (b) (1) Diethyl isopropylmalonate/$TiOEt_4$, 160–190 °C; (2) KOH/EtOH/H_2O, reflux; (c) (1) Quinine, (2) (+)-dehydroabietylamine.

Scheme III[a]



[a] (a) (*S*)-Alpine borane, room temperature; (b) H_2/Lindlar/EtOAc, room temperature; (c) Isovaleryl chloride/NEt_3/DMAP/CH_2Cl_2, room temperature; (d) LICA/TMS-Cl/THF, −78 °C, to room temperature.

(4) (a) Holladay, M. W.; Salituro, F. G.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 374. (b) Fray, A. H.; Kaye, R. L.; Kleinman, E. F. *J. Org. Chem.* **1986**, *51*, 4828. (c) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. (d) Kempf, D. J. *J. Org. Chem.* **1986**, *51*, 3921. (e) Hester, J. B.; Pals, D. T.; Saneii, H. H.; Sawyer, T. K.; Schostarez, H. J.; Tenbrink, R. E.; Thaisrivongs, S. European Patent Application EP 173481, 1986.

(5) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079.

(6) Bühlmayer, P.; Caselli, A.; Fuhrer, W.; Göschke, R.; Rasetti, V.; Rüeger, H.; Stanton, J. L.; Criscione, L. Wood, J. M. *J. Med. Chem.* **1988**, *31*, 1839.

(7) Carroll, M. F. *J. Chem. Soc.* **1941**, 507.

(8) A variety of alkyl- and hetero-substituted malonates were found to undergo transesterification reactions with allylic alcohols and subsequent Carroll rearrangements catalyzed by $Ti(OEt)_4$. Herold, P., unpublished work.

(9) Ee values were determined by HPLC analysis of the corresponding (+)-phenethylamine derivatives, cf. Experimental Section.

(10) For the determination of the absolute configuration see below.

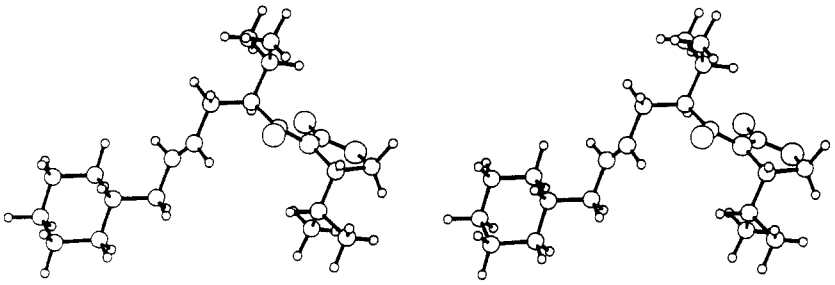
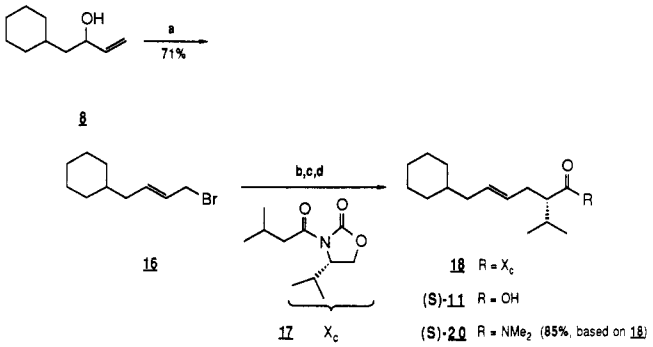


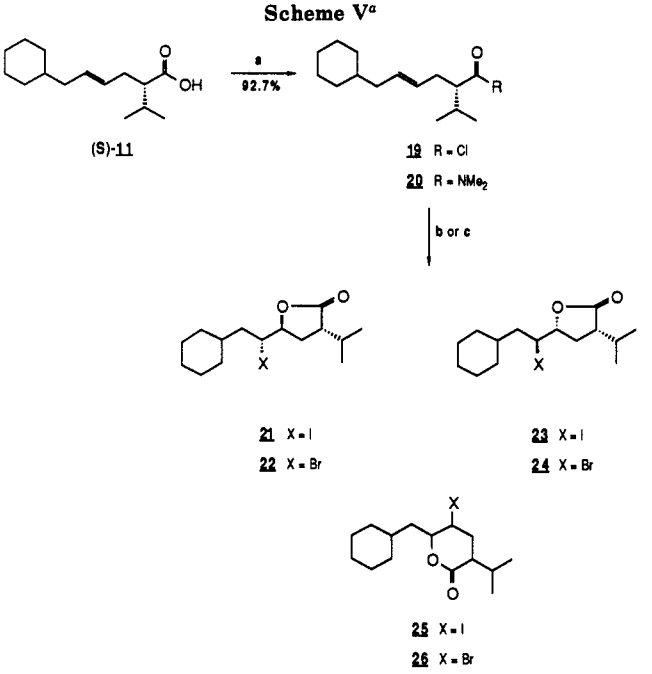
Figure 1. Computer-generated stereo drawing of imide 18, based on X-ray diffraction data.

Scheme IV[a]



[a] (a) $SOBr_2$/1,5-hexadiene/$ClCH_2CH_2Cl$, 0 °C; (b) (1) LDA/17/THF, −78 °C; (2) 16, −78 to 0 °C; (c) H_2O_2/LiOH/THF–H_2O, room temperature; (d) (1) $(COCl)_2$/toluene, reflux, (2) $(CH_3)_2NH$/pyridine/CH_2Cl_2, 0 °C to room temperature.

Scheme V[a]



[a] (a) (1) $(COCl)_2$/toluene, reflux, (2) $HNMe_2$/pyridine/CH_2Cl_2, 0 °C; (b) I_2/AcOH/THF/H_2O, 0 °C; (c) NBS/AcOH/THF/H_2O, 0 °C.

the mother liquor with (+)-dehydroabietylamine afforded (−)-11 of 90% ee.[9-11]

Next we focused our attention on an asymmetric version of the above reaction sequence. For this study we prepared optically active (*S*)-11 by asymmetric reduction of alkynone 12[12] with commercially available (*S*)-Alpine borane (82% ee)[13] followed by semihydrogenation of the resulting propargylic alcohol 13 (80% ee)[14] over Lindlar's catalyst (Scheme III). In order to effect optimal 1,4 chirality transfer, the subsequent Claisen rearrangement was carried out according to Ireland.[16] Conversion of compound (*S*)-8 to the corresponding isovaleric ester 14 (93% yield) was followed by enolization and silylation with lithium cyclohexylisopropylamide and TMS-Cl at −78 °C. The resulting (*E*)-silylketene acetal 15 was allowed to rearrange at room temperature to afford the unsaturated carboxylic acid (−)-11 in 97% yield and 78% ee.[9,10,17] From the high chirality transfer observed in the Ireland–Claisen rearrangement, it can be calculated that if one were to start with optically pure (*S*)-Alpine borane,[19] (−)-11 would be obtained in >95% ee.

Chart I

halogen	$\gamma_{(trans)}$:$\gamma_{(cis)}$:δ[1]	$\gamma + \delta$ (%)[2]	$\gamma_{(trans)}$ (%)[3]
I	20:2:1	95	75
Br	20:1:2	90	60

[1] Determined by HPLC. [2] Isolated yield. [3] Isolated by crystallization.

A more direct access to (−)-11 of high optical purity was finally found by application of the stereoselective alkylation methodology introduced by Evans et al.[20] Bromination of alcohol 8 with $SOBr_2$ under conditions favoring allylic rearrangement gave the bromide 16 containing ca. 10% of its allylic isomer (Scheme IV). The alkylation of the chiral imide 17 with bromide 16 proceeded very slowly at −78 °C (65% yield, 87% conversion after 3 days). A complete conversion within 20 h without affecting the yield and diastereoselectivity was possible, however, when the temperature of the reaction mixture was gradually raised to 0 °C. Crystallization gave 61% of 18 (99.5% ds) and

(11) (*R*)-11 can be recycled to *rac*-11 by esterification, base treatment (KOt-Bu/H_2O (2:1), ether) and subsequent hydrolysis.

(12) (a) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45. (b) Giacomelli, G.; Rosini, C.; Caporusso, A. M.; Palla, F. *J. Org. Chem.* **1983**, *48*, 4887.

(13) (a) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1380. (b) Hawkins, J. M.; Sharpless, K. B. *Org. Synth.* **63**, 57.

(14) Ee values were determined by ^1H NMR spectroscopy after derivatization with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride.[15]

(15) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(16) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

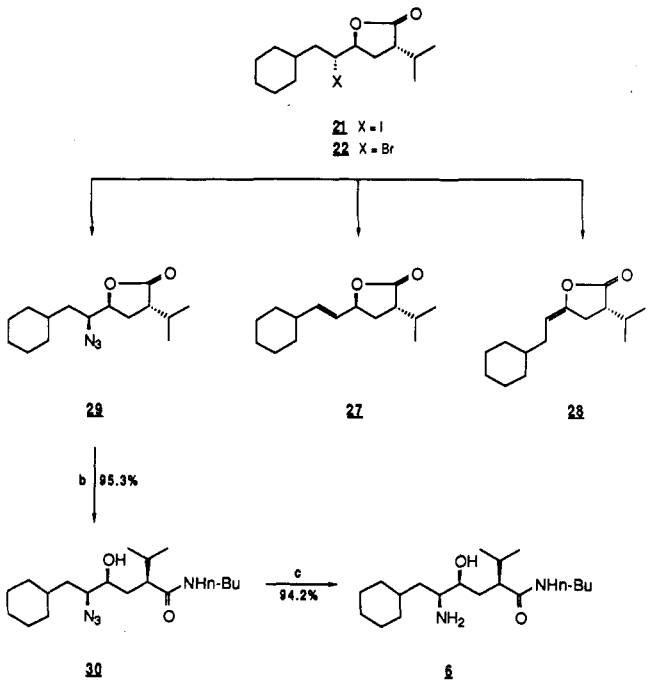
(17) In a related case reported by Nakai et al.[18] the authors point out the importance of using a sterically demanding silyl group in order to achieve a high degree of 1,4 chirality transfer in the Claisen rearrangement. In our case equally high enantioselectivities are observed with the sterically less demanding trimethylsilyl group because of the presence of the bulky isopropyl substituent at C-2.

(18) Nagatsuma, M.; Shirai, F.; Sayo, N.; Nakai, T. *Chem. Lett.* **1984**, 1393.

(19) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Org. Chem.* **1982**, *47*, 4583.

(20) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

Scheme VI[a]



[a] (a) NaN_3/DMPU, room temperature; (b) *n*-butylamine, 40 °C; (c) H_2/Pd-C/methanol, room temperature.

Chart II

halolactone	29:28:27[1]	27 + 28 + 29 (%)[2]	29 (%)[2]
21	4.5:8:1	95	27
22	20:5.5:1	95	72

[1] Determined by ^1H NMR. [2] Isolated Yield.

12% of **18** from the mother liquor (96.8% ds). The diastereoface differentiation of this alkylation was therefore ca.99:1.[21] This sequence was then completed by the cleavage of the imide with Li hydroperoxide[20b] to give ca. 93% of (−)-**11** and the chiral auxiliary "X_c" (Scheme IV). Not unexpectedly imide **18** was completely unreactive toward LiOH. Since the purification of (−)-**11** is rather tedious, it is preferable to continue the sequence with the crude reaction mixture. The amide **20** is thereby obtained in 85% overall yield from imide **18**.

According to the induction rules for "Alpine-borane" reductions[13] and for imide alkylations,[20a] the *S* configuration of (−)-**11** can be deduced with a high degree of confidence. This also implies a chairlike transition state for the Ireland–Claisen rearrangement. An unambiguous confirmation is provided by the X-ray analysis of the crystalline imide **18** shown in Figure 1. The 2*S* configuration of the hexenoate could be related to the known 4*S* configuration of the heterocycle in **18**.

With efficient routes for the preparation of essentially enantiomerically pure (*S*)-**11** at hand, our attention was directed to the conversion of (*S*)-**11** to the final hydroxyethylene dipeptide isostere **6** (Schemes V and VI). For the key diastereoselective halo lactonization reaction, (*S*)-**11** was converted to the corresponding dimethylamide **20** via the acid chloride (**19**). Initial attempts to achieve iodo lactonization by the procedure recommended by Yoshida[5] resulted in an extremely slow and incomplete formation of the desired γ-lactone **21**.[22] After extensive experimentation it was found that this process could be effectively accelerated by the addition of an equivalent of acetic acid relative to the amount of iodine employed. Cyclization led, as expected, predominantly to the thermodynamically more stable trans disubstituted γ-lactone **21** (Scheme V). Minor amounts of the cis isomer **23** as well as the δ-lactone **25**, resulting from a 6-endo-trigonal cyclization reaction,[24] were easily removed by crystallization, thereby affording diastereomerically pure **21** in 75% yield. In an analogous manner bromo lactonization of **20** yielded *trans*-bromo lactone **22** with comparable diastereoselectivity (Scheme V). Again the major cyclization product was easily purified by crystallization. The stereochemistry of the bromo lactones **22** and **24** was assigned by their characteristic coupling pattern in the ^1H NMR[25] spectrum (cf. Experimental Section). δ-Lactones **25** and **26**, which were exclusively formed as single diastereomers, exhibit IR absorption bands at 1745 cm^{-1} and can be differentiated unambiguously from their 5-membered ring analogues.

Treatment of iodo lactone **21** with azide under a variety of reaction conditions was found to give predominantly the elimination products **27** and **28** and not as expected the substitution product **29** (Scheme VI). Surprisingly, however, under identical reaction conditions the corresponding bromo lactone **22** afforded predominantly the desired azido lactone **29** (Scheme VI). Removal of the minor byproducts **27** and **28** by crystallization yielded diastereomerically pure **29** in 67%.[26] At this stage the stereochemical integrity of the trans substituted γ-lactone **29** was verified by comparison of the ^1H NMR coupling constants of the lactone ring protons with those of the corresponding bromo and iodo lactones **21** and **22**, respectively (cf. Experimental Section). Since **29** was obtained as a single diastereomer, it seems plausible to assume that azide substitution of **22** took place with inversion of configuration at C-5. Ring opening of lactone **29** was achieved in neat *n*-butylamine at 40 °C with no detectable epimerization at C-2. Hydrogenation of the resulting azide **30** then gave our target dipeptide isostere **6** as a crystalline material in 89% overall yield from **29**. A confirmation of the structure of **6** was obtained by comparison with an authentic material, which was prepared by a different route from (L)-cyclohexylalanine.[6] Synthesis of peptide analogues containing the hydroxyethylene dipeptide isostere **6** and their biological activities are reported elsewhere.[6]

Conclusions

An efficient and diastereoselective synthesis of the hydroxyethylene dipeptide isostere **6** has been developed. The desired chirality at C-2 was introduced by an asymmetric alkylation procedure or alternatively by asymmetric reduction of alkynone **12** followed by a stereocontrolled Ireland–Claisen rearrangement. The key intermediate (*S*)-**11** was also obtained by a simple chemical resolution procedure. Introduction of the correct configurations at C-4 and C-5 was achieved by a diastereoselective bromo lactonization reaction followed by S_N2 substitution at C-5 with azide. This method is unique in the sense that none of the starting materials are derived from amino acids. This makes the synthesis extremely versatile, allowing broad variations of substituents at C-2 and C-5.[27] In

(21) The diastereomer ratios (ds) of **18** correspond to the optical purities determined for the acid **11**[9] obtained from **18**.

(22) Iodolactinization of the free carboxylic acid leads predominantly but with lower diastereoselectivity to the cis-disubstituted γ-lactone **23**.[23]

(23) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950.

(24) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(25) Tayyeb Hussain, S. A. M.; Ollis, W. D.; Smith, S.; Fraser Stoddart, J. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1480.

(26) Isolation by flash chromatography increases the yield of **29** to 72%.

(27) Herold, P.; Angst, Ch. European Patent Application EP 258183, 1987.

addition, preparation of the hydroxyethylene dipeptide isostere **6** does not require any chromatographic separation, thereby making **6** accessible in large quantities.

Experimental Section

Water-sensitive reactions were carried out in flame-dried glassware under argon. THF, Et_2O, and toluene were distilled over Na/benzophenone prior to use. Solutions were dried with $MgSO_4$ and evaporated below 50 °C in a Büchi rotary evaporator. TLC: Merck precoated silica gel 60 F-254 plates; detection by UV, $KMnO_4$, or phosphomolybdic acid. Flash chromatography (FC):[28] silica gel Merck 60 (40–63 μm). HPLC analyses have been carried out either on a Kontron HPLC-system 600 with UV detection (ERC-7210 of Erma optical works) or on a Spectra Physics system with UV detection (SP 8773 XR) using analytical columns (250 × 5 mm) filled with 5-μm silica gel (Spherisorb SW or Spherisorb Si 80). The separations were done at a constant flow rate. Melting point (uncorrected): Büchi-510 apparatus. Optical rotations: Perkin-Elmer-241 polarimeter. IR: Perkin-Elmer-298 spectrometer. ^1H NMR and ^{13}C NMR: Bruker AM-300, Bruker AM-360 and Varian XL-300 instrument; chemical shifts (δ) are indicated in ppm relative to TMS as internal standard; coupling constants (*J*) are given in hertz.

1-Cyclohexyl-3-buten-2-ol (8). A solution of cyclohexanecarboxaldehyde (**7**) (60 g, 0.47 mol) in dry THF (400 mL) was added dropwise to a solution of vinylmagnesium bromide in dry THF (1 M, 570 mL, 0.57 mol) at −20 °C. After the mixture was stirred at −20 °C for 0.5 h, saturated NH_4Cl (900 mL) was added, and the mixture allowed to warm to room temperature. After dilution with H_2O (250 mL) and extraction with Et_2O, the organic layer was washed with saturated NaCl, dried, and evaporated in vacuo. Distillation (64 °C, 7 mbar) afforded **8** (63.6 g, 87%) as a colorless oil: IR (CH_2Cl_2) 3600, 3040, 2920, 2850, 1450; ^1H NMR ($CDCl_3$) δ 0.83–1.02 (m, 2 H), 1.07–1.55 (m, 7 H), 1.58–1.84 (m, 5 H), 4.13–4.28 (m, H-C(2)), 5.10 (d, *J* = 10, H-C(4)), 5.23 (d, *J* = 17.5, H-C(4)), 5.87 (ddd, *J* = 17.5, 10, 6.5, H-C(3)). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.77. Found: C, 77.62; H, 11.54.

(*E*)-6-Cyclohexyl-2-(1-methylethyl)-4-hexenoic Acid (11). A mixture of **8** (23.15 g, 0.15 mol), $TiOEt_4$ (3.42 g, 15 mmol), and diethyl isopropylmalonate (33.8 mL, 0.165 mol) was stirred at 160 °C for 1 h and at 190 °C for 4 h, distilling off ethanol formed; 6 N KOH (120 mL) and ethanol (120 mL) were added, and the mixture was refluxed for 7 h. After filtration and concentration in vacuo, the aqueous layer was extracted with Et_2O, acidified (pH = 1) with 6 N HCl, and extracted again with Et_2O. The combined organic layers were washed with saturated NaCl, dried, and evaporated in vacuo. Distillation (140 °C, 0.02 mbar) yielded **11** (30.6 g, 85.7%) as a colorless oil: IR (CH_2Cl_2) 3070, 2960, 2920, 2840, 1700, 1440; ^1H NMR ($CDCl_3$) δ 0.76–0.93 (m, 2 H), 0.95 and 0.97 (2 d, *J* = 7.5, 2 CH_3), 1.06–1.30 (m, 4 H), 1.58–1.75 (m, 5 H), 1.81–1.97 (m, 3 H), 2.15–2.35 (m, 3 H), 5.33 and 5.48 (2 dt, *J* = 15, 6, H-C(4) and H-C(5)). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.49; H, 10.91.

(2*S*)-1-Cyclohexyl-3-butyn-2-ol (13). A round-bottomed flask was charged, via a double-ended needle, with (*S*)-Alpine borane (Aldrich, 82% ee, 0.5 M in THF, 185 mL, 92.5 mmol), and most THF was removed by water aspirator vacuum. The neat organoborane was obtained by applying a 0.05-mbar vacuum for 2 h while warming to 40 °C with a water bath.[13] The flask was cooled to 0 °C, and **12** (10 g, 66 mmol), prepared from cyclohexylacetic acid,[12] was added. The ice bath was removed, and the mixture was stirred at room temperature for 20 h. Propionaldehyde (6.6 mL, 92.5 mmol) was then added dropwise and stirring was continued for 1 h. Liberated α-pinene was removed in vacuo (0.05 mbar, 50 °C, 3 h) and to the mixture were added THF (50 mL) and 3 M NaOH (35 mL), followed by 30% H_2O_2 (35 mL) below 40 °C. After being stirred at 40 °C for 2 h, the mixture was extracted with Et_2O. The extracts were washed with saturated NaCl and dried, and the solvent was evaporated in vacuo. The residue was purified by Kugelrohr distillation (80 °C, 0.01 mbar), yielding pure **13** (8.13 g, 80.4%) as a colorless oil of 80% ee:[14] $[\alpha]^{25}_D$ −8.1° (*c* = 0.9, $CHCl_3$); IR (neat) 3360, 3300, 2920, 2850, 1685, 1450; ^1H NMR ($CDCl_3$) δ 0.83–1.05 (m, 2 H), 1.05–1.35 (m, 3 H), 1.45–1.85 (m, 9 H), 2.45 (d, *J* = 2, H-C(4)), 4.45 (dt, *J* = 8, 2, H-C(2)). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.60. Found: C, 78.73; H, 10.83.

(2*S*)-1-Cyclohexyl-3-buten-2-ol ((*S*)-8). Compound **13** (10 g, 66 mmol, 80% ee) was dissolved in EtOAc (100 mL), Lindlar's catalyst (Fluka, 1 g) was added, and the mixture was shaken under 1 atm of H_2 for 40 min. The catalyst was removed by filtration through Celite, and the solvent was evaporated in vacuo. The residue was purified by distillation (55 °C, 0.6 mbar), yielding (*S*)-**8** (8.0 g, 79%) as a colorless oil. The spectroscopic data are identical with those described for the corresponding racemic compound.

(2*S*)-1-Cyclohexyl-3-buten-2-yl 3-Methylbutanoate (14). Isovaleryl chloride (3.2 ml, 26 mmol) was added to a solution of (*S*)-**8** (3.56 g, 23 mmol), NEt_3 (4 mL, 28 mmol), and DMAP (288 mg, 2.4 mmol) in CH_2Cl_2 (70 mL) at 0 °C. The mixture was stirred at room temperature overnight, diluted with Et_2O and washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl. After drying and evaporation in vacuo the residue was purified by Kugelrohr distillation (80 °C, 0.02 mbar), affording **14** (5.1 g, 92.7%) as a colorless oil: $[\alpha]^{25}_D$ −13.6° (*c* = 1, $CHCl_3$); IR (neat) 3080, 2960, 2920, 2870, 2850, 1735, 1465, 1450; ^1H NMR ($CDCl_3$) δ 0.80–1.05 (m, 1 H), 0.98 (d, *J* = 6, 2 CH_3), 1.05–1.45 (m, 5 H), 1.45–1.85 (m, 7 H), 2.04–2.26 (m, 3 H), 5.14 (d, *J* = 10, H-C(4)), 5.23 (d, *J* = 17.5, H-C(4)), 5.30–5.42 (ddd, *J* = 6, H-C(2)), 5.78 (ddd, *J* = 17.5, 10, 6, H-C(3)). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00; O, 13.43. Found: C, 75.40; H, 11.26; O, 13.41.

(*E*)-4-Bromo-1-cyclohexyl-2-butene (16). To a solution of **8** (2 g, 13 mmol) and 1,5-hexadiene (0.8 g, 9.7 mmol) in 1,2-dichloroethane (25 mL) was added carefully $SOBr_2$ (1.5 mL, 4.0 g, 19.5 mmol) at 0–3 °C. After the mixture was stirred at 0 °C for 1 h, the reaction was quenched by the addition of H_2O (24 mL) and stirred at 0 °C for 15 min. The mixture was extracted with Et_2O, and the extracts were washed with ice–H_2O and cold saturated $NaHCO_3$. The solvent was dried and evaporated in vacuo, and the residue was purified by FC (hexane) and by Kugelrohr distillation (100–120 °C, 0.2 mbar) yielding **16** (2.02 g, 71%), containing, according to ^1H NMR, ca. 10% of 2-bromo-1-cyclohexyl-3-butene: IR (neat) 3020, 2910, 2840, 1655, 1445, 1205, 965; ^1H NMR ($CDCl_3$) δ 0.80–1.00 (m, 2 H), 1.05–1.40 (m, 4 H), 1.55–1.80 (m, 5 H), 1.95 (t, *J* = 7, 2 H-C(1)), 3.95 (d, *J* = 7, 2 H-C(4)), 5.66 and 5.76 (2 dt, *J* = 15 and 7, H-C(2), H-C(3)); signals of the allylic isomer 4.60 ("q"), 5.05 (d, *J* = 11), 5.32 (d, *J* = 16), 5.99 (ddd, *J* = 16, 11, 9) (1 H each). Anal. Calcd for $C_{10}H_{17}Br$: C, 55.31; H, 7.89; Br, 36.80. Found: C, 54.89; H, 7.92; Br, 37.26.

(4*S*)-*N*-(3-Methylbutanoyl)-4-(1-methylethyl)-2-oxazolidinone (17). To a solution of (4*S*)-4-isopropyl-2-oxazolidinone (39.55 g, 0.306 mol) in dry THF (1.02 L) was added *n*-BuLi (Fluka, 1.6 N in hexane, 200 mL, 0.32 mol) below −66 °C. After the mixture was stirred at −78 °C for 15 min, isovaleroyl chloride (40.7 mL, 0.33 mol) was added, and the mixture was stirred at 0 °C for 1 h. The reaction was then quenched by the addition of 1 M K_2CO_3 (200 mL) and the solvent was evaporated at reduced pressure after the mixture had been stirred at room temperature for 1 h. H_2O was added, and the mixture was extracted with Et_2O. The extracts were washed with saturated NaCl, dried, and concentrated in vacuo. Distillation of the residue (79–89 °C, 0.015 mbar) afforded pure **17** (62.02 g, 95%). $[\alpha]^{25}_D$ +76.4° (*c* = 1.29, $CHCl_3$); IR (neat) 2960, 2870, 1783, 1705, 1390, 1375, 1308, 1210; ^1H NMR ($CDCl_3$) δ 0.87, 0.89, 0.98, and 1.00 (4 d, *J* = 7), and 2.19 (hept, *J* = 7) and 2.37 (hept d, *J* = 7, 4) (2 $(CH_3)_2CH$), 2.72 (dd, *J* = 18, 8) and 2.96 (dd, *J* = 18, 7) (2 H-C(2′)), 4.17 (dd, *J* = 9, 4) and 4.25 (dd, *J* = 9, 8, 2 H-C(5)), 4.45 (dt, *J* = 8, 4, H-C(4)). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.95; H, 9.10; N, 6.37.

(4′*E*,4*S*,2′*S*)-*N*-[6′-Cyclohexyl-2′-(1-methylethyl)-4′-hexenoyl]-4-(1-methylethyl)-2-oxazolidinone (18). *n*-BuLi (Fluka, 1.6 N in hexane, 20 mL, 31 mmol) was added dropwise to a solution of diisopropylamine (4.8 mL, 33.8 mmol) in dry THF (70 mL) at −20 °C. After the mixture was stirred at −20 °C for 15 min, **17** (6.11 g, 28.65 mmol) in a small amount of THF was added below −65 °C. After the reaction mixture was stirred at −78 °C for 2 h, dimethylpropyleneurea (DMPU) (7.8 mL) followed by bromide **16** (6.73 g, 31 mmol) was added at −78 °C. The mixture was stirred at −78 °C for 1 h and then allowed to warm to 0 °C within 20 h. After 15 min at room temperature the reaction was

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Table I. Single-Crystal X-ray Crystallographic Analysis

formula	$C_{21}H_{35}NO_3$
crystallization medium	CH_3OH
crystal size	0.8 × 0.3 × 0.07
cell dimension	
a, Å	20.568 (5)
b, Å	6.410 (3)
c, Å	16.461 (2)
β, deg	95.57 (2)
g, Å	2160 (2)
space group	*C*2
Z	4
calcd density, g/cm^3	1.075
number of reflections	2506
nonzero reflections ($I > 2\sigma$)	2293
number of parameters	365
final *R* factor	0.081
max residual electron density, e/Å^3	0.388

quenched by the addition of saturated NH_4Cl (120 mL) under ice cooling (0–10 °C). The mixture was extracted with Et_2O, and the organic layers were washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl, dried, and evaporated in vacuo. FC (hexane/EtOAc, 6:1) and crystallization of the pure fractions (7.54 g, 75%) from hexane gave 6.51 g (61%) of **18** (ca. 99.5% ds)[21] and 1.24 g (12%) of **18** (ca. 96.8% ds)[21] from the mother liquor: mp 68–68.5 °C; $[\alpha]^{25}_D$ +58.9° (*c* = 1.0, $CHCl_3$); IR (CH_2Cl_2) 2960, 2920, 2850, 1775, 1695, 1390, 1230, 1210; ^1H NMR ($CDCl_3$) δ 0.75–1.00 (m, 2 H), 0.83, 0.89, 0.905, and 0.915 (4 d, *J* = 7, 2, 2 (CH_3)$_2$CH), 1.05–1.25 (m, 4 H), 1.55–1.70 (m, 5 H), 1.79 (t, *J* = 7, 2H-C(6′)), 1.91 (octett, *J* = 7) and 2.20–2.45 (m, 2 (CH_3)$_2$C*H*, 2 H-C(3′)), 3.78 (ddd, *J* = 9.5, 7.6, 4.5, H-C(2′)), 4.15 (dd, *J* = 9, 3.5) and 4.20 (dd, *J* = 9, 8, 2 H-C(5′)), 4.78 (dt, *J* = 8, 3.5, H-C(4)), 5.29 (ddd, *J* = 16, 7, 6), and 5.42 (dt, *J* = 16, 7, H-C(4′) and H-C(5′)). Anal. Calcd for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 72.24; H, 10.07; N, 4.28. Mother liquor of **18**: ^1H NMR ($CDCl_3$) resolved additional signals due to the (4*S*,2′*R*) diastereomer: 0.82 and 0.88 (2 d, (CH_3)$_2$CH). For the single-crystal X-ray analysis a sample was crystallized from a dilute CH_3OH solution at −15 °C. The crystals were collected on a filter paper and dried in air.

Single-Crystal X-ray Analysis. A colorless needle-shaped crystal was mounted on its log axis parallel to the ψ-axis of the goniometer. An Enraf-Nonius CAD-4 computer-controlled κ-axis diffractometer equipped with a graphite crystal incident beam monochromator and copper radiation was used. All diffractometer data were collected at room temperature. Crystal data are summarized in Table I.

The structure was solved by direct methods (SHELXS program)[29] and refined with Enraf-Nonius SDP.[30] Hydrogen positions were calculated and included in the final cycles of least-squares refinement. The structure was plotted using the PLUTO plotting package[31] (Figure 1). Coordinates, anisotropic temperature factors, distances, and angles are available as supplementary material.

(4*E*,2*S*)-6-Cyclohexyl-2-(1-methylethyl)-4-hexenoic Acid ((*S*)-11). (a) From 11. Compound **11** (154.65 g, 0.65 mol) and anhydrous quinine (210.5 g, 0.65 mol) were dissolved in CH_3OH (1 L). The mixture was evaporated to dryness in vacuo, and the residue was allowed to crystallize with stirring from Et_2O/hexane (1:12, 9 L) at 0 °C. The solid was filtered off and thoroughly washed with hexane yielding (*R*)-**11** (76 g) of 80% ee $[[\alpha]^{25}_D$ +7.2 ° (*c*=1.2, $CHCl_3$)] after treatment with 1 N HCl and extraction with Et_2O. In the same manner (*S*)-**11** (77 g) of 76% ee was isolated from the filtrate. Optically enriched (*S*)-**11** was then dissolved in CH_2Cl_2 (500 mL) and treated with a solution of purified (+)-dehydroabietylamine[32] in CH_2Cl_2 (500 mL). After addition of hexane (4 L) the mixture was refluxed giving a clear solution; 1.2 L of solvent were then distilled off (atm pressure, 41–55 °C), and the salt was allowed to crystallize with stirring at room temperature for 24 h. The solid material was collected by filtration, washed with hexane, and stirred at room temperature for 30 min in the presence of 1 N NaOH (500 mL). H_2O (500 mL) was added, and the mixture extracted four times with Et_2O. The aqueous layer was acidified (pH = 1) with 2 N HCl and extracted again with Et_2O. The combined organic layers were washed with saturated NaCl, dried, and evaporated in vacuo, yielding (*S*)-**11** (58.2 g, 38%) of 90% ee $[[\alpha]^{25}_D$ −8.0° (*c* = 1.25, $CHCl_3$)].

(b) From 14. *n*-BuLi (Fluka, 1.6 N in hexane, 1.5 mL, 2.4 mmol) was added dropwise to a solution of *N*-cyclohexylisopropylamine (distilled CaH_2, 0.43 mL, 2.56 mmol) in dry THF (5 mL) at −20 °C. After the mixture was stirred at −20 °C for 15 min, a solution of **14** (510 mg, 2.14 mmol, 80% ee) and freshly distilled TMS-Cl (0.9 mL, 7.1 mmol) in dry THF (2 mL) was added dropwise at −78 °C. The reaction mixture was allowed to warm to room temperature overnight and quenched by the addition of CH_3OH (0.5 mL) and 1 N NaOH (10 mL) at 0 °C. After the mixture was stirred at room temperature for 15 min and extracted with Et_2O, the aqueous layer was acidified (pH = 1) with 2 N HCl and extracted again with Et_2O. The combined organic layers were washed with saturated NaCl, dried, and evaporated in vacuo. Purification by Kugelrohr distillation (150 °C, 0.02 mbar) afforded (*S*)-**11** (495 mg, 97%) of 77% ee $[[\alpha]^{25}_D$ −7.0° (*c* = 1.2, $CHCl_3$)].

(c) From 18 (Crystals). To a solution of **18** (1.0 g, 2.865 mmol) in THF (42 mL) and H_2O (14 mL) was added H_2O_2 (30%, 1.8 mL, 17 mmol) followed by LiOH (137 mg, 5.72 mmol) at 0–3 °C. The mixture was stirred at room temperature for 55 h and cooled to 0 °C before the addition of 1.5 M $Na_2S_2O_3$ (12.6 mL). THF was evaporated at reduced pressure; the mixture was neutralized by the addition of NaH_2PO_4 (1.4 g) and extracted with EtOAc. Evaporation and FC (hexane/EtOAc, 6:1, + 1% AcOH) of the residue afforded 639 mg of (*S*)-**11** (ca. 93%, ca. 99% ee) containing small amounts of starting material **18**; 320 mg of (*S*)-**11** (ca. 93%, 93.6% ee) were obtained from imid **18** (mother liquor, 500 mg, 1.43 mmol) by using the same procedure.

Determination of the Optical Purity of Acid 11. A solution of **11** (20 mg), (+)-phenethylamine (20 μL), *N*-hydroxybenzotriazole (20 mg), and DCC (25 mg) in DMF (0.6 mL) was stirred at room temperature for 20 h. After the addition of saturated $NaHCO_3$ (3 mL), the mixture was extracted with EtOAc. The residue of the dried organic phase was analyzed by HPLC (hexane/AcOEt, 85:15, 1.5 mL/min, detection at 250 nm) without purification. 2*R* diastereomer: t_R = 7.01 min, 2*S* diastereomer: t_R = 8.52 min.

(4*E*,2*S*)-*N*,*N*-Dimethyl-6-cyclohexyl-2-(1-methylethyl)-4-hexenamide (20). (a) From (*S*)-11. Oxalyl chloride (42.6 mL, 0.49 mol) was added dropwise to a solution of (*S*)-**11** (58.1 g, 0.244 mol) and DMF (0.5 mL) in dry toluene (270 mL), and the reaction mixture was refluxed for 1.5 h. The crude acid chloride **19** obtained upon concentration in vacuo was dissolved in CH_2Cl_2 (270 mL) and added dropwise to a solution of dimethylamine (17.2 g, 0.38 mol) and pyridine (61.4 mL, 0.76 mol) in CH_2Cl_2 at 0 °C. After being stirred at 0 °C for 30 min, the mixture was diluted with Et_2O, washed with 2 N HCl, saturated $NaHCO_3$, and saturated NaCl, dried, and evaporated in vacuo. Distillation (126 °C, 0.04 mbar) of the residue gave **20** (60.0 g, 92.7%) as a colorless oil. **(b) From 18**: Imid **18** (1.0 g, 2.865 mmol) was treated with H_2O_2/LiOH in THF/H_2O for 3 days as described above. The crude reaction mixture obtained by extraction with EtOAc (1.06 g) was then converted to **19** and **20**, respectively, as described above. FC (hexane/EtOAc, 3:1) afforded pure **20** (652 mg, 85%) and recovered starting material **18** (33 mg, 3%): $[\alpha]^{25}_D$ (for a) −4.6° (*c* = 1.4, $CHCl_3$); $[\alpha]^{25}_D$ (for b) −3.4° (*c* = 1.4, $CHCl_3$); IR (CH_2Cl_2) 3030, 2950, 2910, 2840, 1625, 1440; ^1H NMR ($CDCl_3$) δ 0.73–0.90 (m, 2 H), 0.85 (d, *J* = 7, CH_3), 0.95 (d, *J* = 7, CH_3), 1.0–1.3 (m, 4 H), 1.55–1.75 (m, 5 H), 1.75–1.95 (m, 3 H), 2.15–2.35 (m, 2 H), 2.38–2.48 (m, H-C(2)), 2.95 and 3.05 (2 s, NCH_3), 5.28 and 5.43 (dt, *J* = 15, 7, H-C(4) and H-C(5)). Anal. Calcd for $C_{17}H_{31}NO$: C, 76.93; H, 11.77; N, 5.28. Found (for a): C, 76.80; H, 11.85; N, 5.10. Found (for b): C, 76.55; H, 11.83; N, 5.36.

(2*S*,4*S*,5*R*)-6-Cyclohexyl-5-iodo-2-(1-methylethyl)-4-hexanolide (21). To a solution of **20** (530 mg, 2 mmol) and AcOH (0.25 mL, 4.4 mmol) in THF/H_2O (2:1, 12 mL) was added iodine (1.12 g, 4.4 mmol) in THF (8 mL) at 0 °C. After being stirred at 0 °C for 48 h the reaction mixture was poured into ice-cold

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40% $NaHSO_3$ (20 mL) and extracted with Et_2O. The combined organic layers were washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl, dried, and evaporated in vacuo. The residue was filtered through a short pad of silica gel, eluting with Et_2O/hexane (2:1), and concentrated in vacuo, yielding a mixture of **21**, **23**, and **25** (695 mg, 95%). Recrystallization from hexane gave **21** (540 mg, 74%) as a white solid: mp 99–99.5 °C; $[\alpha]^{25}_D$ +35.4° (c = 1.1, $CHCl_3$); IR (CH_2Cl_2) 2960, 2920, 2850, 1770, 1470, 1450; ^{13}C NMR ($CDCl_3$) 177.9 (C(1)), 81.0 (C(4)), 46.1 (C(5)), 42.9 (C(6)), 38.8 and 37.3 (C(2), C(1')), 33.8, 31.5, and 30.1 (C(2'), C(6'), C(3)), 29.5 ($CHMe_2$), 26.5, 26.2, and 25.9 (C(3'), C(4'), C(5')), 20.5 and 18.6 (2 CH_3); ^1H NMR ($CDCl_3$) δ 0.70–0.90 (m, 1 H), 0.90–1.40 (m, 4 H), 0.96 and 1.03 (2 d, J = 7, CH_3), 1.50–1.80 (m, 8 H), 2.1–2.32 (m, 3 H), 2.68 (ddd, J = 10, 6, 5, H-C(2)), 4.16–4.30 (m, H-C(4) and H-C(5)). Anal. Calcd for $C_{15}H_{25}IO_2$: C, 49.46; H, 6.92; O, 8.79; I, 34.84. Found: C, 49.67; H, 7.02; O, 8.74; I, 34.69. Isolated by FC using Et_2O/hexane, 1:8, as eluent. **23**: ^{13}C NMR ($CDCl_3$) δ 177.1 (C(1)), 80.2 (C(4)), 47.0 (C(5)), 43.4 (C(6)), 37.5 and 37.4 (C(2), C(1')), 33.8, 31.6, and 31.4 (C(2'), C(6'), C(3)), 27.7 ($CHMe_2$), 26.5, 26.3, and 25.9 (C(3'), C(4'), C(5')), 20.8 and 18.6 (2 CH_3); ^1H NMR ($CDCl_3$) δ 0.73–1.40 (m, 5 H), 0.96 and 1.06 (2 d, J = 7, CH_3), 1.45–1.85 m, 8 H), 2.15–2.30 (m, 2 H), 2.50 (ddd, J = 13, 9, 6, H_α-C(3)), 2.61 (ddd, J = 12, 9, 5, H-C(2)), 4.07–4.20 (m, H-C(4) and H-C(5)). **25**: IR (CH_2Cl_2) 2965, 2925, 2875, 2855, 1745, 1450; ^{13}C NMR ($CDCl_3$) δ 173.2 (C(1)), 81.1 (C(5)), 43.9 (C(2)), 42.0 (C(6)), 34.0 and 32.1 (C(2'), C(6')), 33.6 (C(1')), 32.1 (C(3)), 27.4 (C(4)), 26.3, 26.1, and 25.8 (C(3'), C(4'), C(5')), 25.2 ($CHMe_2$), 20.2 and 18.4 (2 CH_3); ^1H NMR ($CDCl_3$) δ 0.80–1.32 (m, 5 H), 0.92 and 1.00 (2 d, J = 7, CH_3), 1.50–1.82 (m, 8 H), 2.16–2.42 (m, 3 H), 2.59 (ddd, J = 11, 6.5, 4.5, H-C(2)), 4.18 (ddd, J = 7.5, 4.5, 4.5, H-C(4)), 4.58 (ddd, J = 10, 7.5, 3, H-C(5)). Isomeric ratios were determined by HPLC analysis (hexane/AcOEt, 12:1, 0.5 mL/min, detection at 250 nm) of the crude reaction mixture: t_R (**25**) = 13.87 min, t_R (**21**) = 17.12 min, t_R (**23**) = 22.60 min; **21**:**23**:**25** = 20:2:1.

(2*S*,4*S*,5*R*)-5-Bromo-6-cyclohexyl-2-(1-methylethyl)-4-hexanolide (22). A solution of NBS (88.5 g, 0.5 mol) and AcOH (30 g, 0.5 mol) in THF (1.1 L) was added to **20** (60 g, 0.23 mol) in THF/H_2O (2:1, 1.4 L) at 0 °C within 8 h. After additional stirring at 0 °C for 30 min, the reaction mixture was poured into ice-cold 40% $NaHSO_3$ (1.8 L) and extracted with Et_2O. The combined organic layers were washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl, dried, and evaporated in vacuo. The residue was filtered through silica gel (300 g), eluting with Et_2O/hexane (2:1), and concentrated in vacuo, yielding a mixture of **22**, **24**, and **26** (65 g, 90%). Recrystallization from hexane afforded **22** (43 g, 60%) as a white solid: mp 95–95.5 °C; $[\alpha]^{25}_D$ +35.6° (c = 1.2, $CHCl_3$); IR (CH_2Cl_2) 2960, 2920, 2850, 1775, 1470, 1450; ^{13}C NMR ($CDCl_3$) δ 177.7 (C(1)), 80.0 (C(4)), 56.1 C((5)), 45.5 (C(2)), 41.8 (C(6)), 35.1 (C(1')), 33.8 and 31.5 (C(2'), C(6')), 29.2 ($CHMe_2$), 27.4, 26.3, 26.1, and 25.8 (C(3), C(3'), C(4'), C(5')), 20.3 and 18.4 (2 CH_3); ^1H NMR ($CDCl_3$) δ 0.73–1.35 (m, 5 H), 0.95 and 1.02 (2 d, J = 7, CH_3), 1.50–1.83 (m, 8 H), 2.06–2.31 (m, 3 H), 2.68 (ddd, J = 10, 7.5, 5, H-C(2)), 4.16 (ddd, J = 10, 6, 5, H-C(5)), 4.43 (ddd, J = 8, 6, 6, H-C(4)). Anal. Calcd for $C_{15}H_{25}BrO_2$: C, 56.79; H, 7.94; Br, 25.19. Found: C, 56.94; H, 8.04; Br, 25.22. Isolated by FC using Et_2O/hexane, 1:8, as eluant. **24**: ^{13}C NMR ($CDCl_3$) δ 176.9 (C(1)), 79.3 (C(4)), 55.1 (C(5)), 46.5 (C(2)), 42.1 (C(6)), 35.0 (C(1')), 33.8 and 31.4 (C(2'), C(6')), 28.8 ($CHMe_2$), 27.5, 26.3, 26.1, and 25.8 (C(3), C(3'), C(4'), C(5')), 20.5 and 18.2 (2 CH_3); ^1H NMR ($CDCl_3$) δ 0.75–1.38 (m, 5 H), 0.95 and 1.06 (2 d, J = 7, CH_3), 1.50–1.90 (m, 8 H), 1.91 (ddd, J = 13, 9, 6, H_β-C(3)), 2.15–2.31 (m, 1 H, C*H*CH_3), 2.42 (ddd, J = 13, 9, 6, H_α-C(3)), 2.62 (ddd, J = 12, 9, 5, H-C(2)), 4.10 (ddd, J = 11, 7, 3.5, H-C(5)), 4.30 (ddd, J = 10, 7, 6, H-C(4)). **26**: IR (CH_2Cl_2) 2960, 2920, 2850, 1745, 1450; ^{13}C NMR ($CDCl_3$) δ 172.9 (C(1)), 79.8 (C(5)), 47.4 (C(4)), 42.6 (C(2)), 41.6 (C(6)), 34.0 and 32.2 (C(2'), C(6')), 33.4 (C(1')), 29.7 (C(3)), 27.4 ($CHMe_2$), 26.3, 26.1, and 25.8 (C(3'), C(4'), C(5')), 20.2 and 18.3 (2 CH_3); ^1H NMR ($CDCl_3$) δ 0.70–1.35 (m, 5 H), 0.94 and 1.02 (2 d, J = 7, CH_3), 1.50–1.85 (m, 8 H), 2.15–2.42 (m, 3 H), 2.67 (ddd, J = 11, 7.5, 4.5, H-C(2)), 4.12 (ddd, J = 7, 5, 5, H-C(4)), 4.5 (ddd, J = 9.5, 7, 2.5, H-C(5)). Isomeric ratios were determined by HPLC analysis (hexane/AcOEt, 12:1, 0.5 mL/min, detection at 250 nm) of the crude reaction mixture: t_R (**26**) = 13.84 min, t_R (**22**) = 17.21 min, t_R (**24**) = 21.14 min; **22**:**24**:**26** = 20:1:2.

(2*S*,4*S*,5*S*)-5-Azido-6-cyclohexyl-2-(1-methylethyl)-4-hexanolide (29). (a) From 22. A solution of **22** (42.5 g, 0.135 mol) in dimethylpropyleneurea (DMPU) (480 mL) was treated with NaN_3 (10.5 g, 0.16 mol) and stirred at room temperature for 72 h. The reaction mixture was poured into ice–H_2O (1 L) and extracted with Et_2O. The combined organic layers were washed with H_2O and saturated NaCl, dried, and evaporated in vacuo. The residue (34.6 g, ca. 95%) was recrystallized from hexane, yielding **29** (25.2 g, 67.3%) as a white solid. The overall yield was improved (27 g, 72%) by FC (hexane/Et_2O, 4:1) and subsequent recrystallization (hexane) of the material obtained from the mother liquor.

(b) From 21. By use of the reaction conditions described above, treatment of **21** (500 mg, 1.44 mmol) with NaN_3 gave 340 mg (ca. 95%) of crude material. Pure **29** (110 mg, 27%) was obtained by FC (hexane/Et_2O, 4:1) and subsequent recrystallization (hexane): mp 38.5–39 °C; $[\alpha]^{25}_D$ +25.1° (c = 0.87, $CHCl_3$); IR (CH_2Cl_2) 2960, 2930, 2850, 2120, 1775, 1540, 1520; ^{13}C NMR ($CDCl_3$) δ 177.8 (C(1)), 79.5 (C(4)), 62.5 (C(5)), 45.2 (C(2)), 37.6 (C(6)), 34.2 (C(1')), 33.7 and 32.7 (C(2'), C(6')), 29.1 ($CHMe_2$), 26.9, 26.4, and 26.2 (C(3'), C(4'), C(5')), 26.0 (C(3)), 20.4 and 18.4 (2 CH_3); ^1H NMR ($CDCl_3$) δ 0.85–1.05 (m, 2 H), 0.93 and 1.02 (2 d, J = 7, CH_3), 1.07–1.34 (m, 3 H), 1.38–1.85 (m, 8 H), 2.05–2.25 (m, 3 H), 2.70 (ddd, J = 10, 7.5, 5, H-C(2)), 3.40 (dt, J = 9, 4, H-C(5)), 4.41 (ddd, J = 7.5, 6, 4, H-C(4)). Anal. Calcd for $C_{15}H_{25}N_3O_2$: C, 64.49; H, 9.02; N, 15.04. Found: C, 64.53; H, 8.96; N, 15.04. Isolated by FC using hexane/Et_2O, 4:1, as eluant. **27**: ^1H NMR δ 0.80–1.80 (m, 14 H), 0.93 and 1.02 (2 d, J = 7, 2 CH_3), 1.90–2.06 (m, 2 H), 2.08–2.30 (m, 2 H), 2.55 (ddd, J = 9.5, 8, 5, H-C(2)), 4.85 (ddd, J = 8, 8, 6, H-C(4)), 5.40 and 5.70 (2 dd, J = 15, 7, H-C(5) and H-C(6)). **28**: 0.80–1.80 (m, 11 H), 0.93 and 1.02 (2 d, J = 7, 2 CH_3), 1.86 (dd, J = 7.5, 2 H-C(7)), 2.13–2.28 (m, 1 H, C*H*$(CH_3)_2$), 2.41 (dd, J = 15, 5, H_β-C(4)), 2.83 (ddd, J = 10, 5, H-C(3)), 2.95 (dd, J = 15, 10, H_α-C(4)), 5.18 (dt, J = 7.5, 2.5, H-C(6)). Isomeric ratios were determined by ^1H NMR analysis of the corresponding crude reaction mixtures: (for a) **29**:**28**:**27** = 20:5.5:1; (for b) **29**:**28**:**27** = 4.5:8:1.

(2*S*,4*S*,5*S*)-*N*-Butyl-5-azido-6-cyclohexyl-4-hydroxy-2-(1-methylethyl)hexanamide (30). Compound **29** (83.8 g, 0.3 mol) was dissolved in *n*-butylamine (840 mL) and stirred at 40 °C for 24 h. Evaporation of excess amine in vacuo and recrystallization of the residue from cyclohexane afforded **30** (92.2 g, 87.2%) as a white solid. The overall yield was improved (100.8 g, 95.3%) by FC (hexane/EtOAc, 2:1) and subsequent recrystallization (cyclohexane) of the material obtained from the mother liquor: mp 100–100.5 °C; $[\alpha]^{25}_D$ −28.0° (c = 0.94, $CHCl_3$); IR (CH_2Cl_2) 3550, 3430, 3320, 3040, 2960, 2920, 2870, 2100, 1660, 1640, 1520; ^{13}C NMR ($CDCl_3$) δ 175.4 (C(1)), 71.8 (C(4)), 65.1 (C(5)), 51.2 (C(2)), 39.3 (C(1'')), 38.5 and 34.8 (C(3), C(6)), 34.6 (C(1')), 34.1 and 32.6 (C(2'), C(6')), 31.8 (C(2'')), 30.3 ($CHMe_2$), 26.6, 26.4, and 26.2 (C(3'), C(4'), C(5')), 21.3 and 20.5 (2 CH_3), 20.2 (C(3'')), 13.9 (C(4'')); ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 8.5, CH_3), 0.92 and 0.95 (2 d, J = 5, CH_3), 0.9–2.0 (m, 20 H), 2.05 (ddd, J = 10, 9, 4, H-C(2)), 2.10–2.75 (br, OH), 3.15–3.38 (m, 3 H, H-C(5) and N-CH_2), 3.48 (ddd, J = 7, 4, 2.5, H-C(4)), 5.68 (t, J = 5, NH). Anal. Calcd for $C_{19}H_{36}N_4O_2$: C, 64.74; H, 10.29; N, 15.89. Found: C, 65.06; H, 10.40; N, 15.89.

(2*S*,4*S*,5*S*)-*N*-Butyl-5-amino-6-cyclohexyl-4-hydroxy-2-(1-methylethyl)hexanamide (6). Compound **30** (21.3 g, 60 mmol) was dissolved in CH_3OH (240 mL) and shaken under 1 atm of H_2 for 2 h in the presence of 10% Pd/C (2.0 g). The catalyst was removed by filtration through Celite and washed with CH_3OH, and the solvent was evaporated in vacuo. Recrystallization from hexane gave **6** (17.64 g, 89.5%) as a white solid. The overall yield was improved (18.56 g, 94.2%) by FC (CH_2Cl_2/CH_3OH/NH_3, 350:50:1) and subsequent recrystallization (hexane) of the material obtained from the mother liquor: mp 88–89 °C; $[\alpha]^{25}_D$ −27.4° (c = 1.1, $CHCl_3$); IR (CH_2Cl_2) 3440, 3045, 2960, 2920, 2870, 2850, 1665, 1520; ^{13}C NMR ($CDCl_3$) δ 175.3 (C(1)), 72.0 (C(4)), 53.3 (C(5)), 51.3 (C(2)), 42.4 (C(6)), 39.1 (C(1'')), 35.2 (C(3)), 34.6 and 32.5 (C(2'), C(6')), 34.5 (C(1')), 31.9 (C(2'')), 30.6 ($CHMe_2$), 26.7, 26.5, and 26.3 (C(3'), C(4'), C(5')), 21.3 and 20.5 (2 CH_3), 20.2 (C(3'')), 13.9 (C4'')); ^1H NMR ($CDCl_3$) δ 0.70–1.80 (m, 23 H), 0.91 (t, J = 8.5, CH_3), 0.91 and 0.94 (2 d, J = 5, CH_3), 1.80–1.95 (m, 1 H), 2.08 (ddd, J = 10, 8, 3.5, H-C(5)), 3.07 (ddd, J = 8.5, 6, 2.5, H-C(4)), 3.16–3.37 (m, NCH_2), 5.76 (t, J = 5, NH). Anal.

Calcd for $C_{19}H_{38}N_2O_2$: C, 69.89; H, 11.73; N, 8.58. Found: C, 70.00; H, 11.61; N, 8.35.

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Supplementary Material Available: Crystallographic data including tables of coordinates, anisotropic temperature factors, distances, and bond angles for **18** (6 pages). Ordering information is given on any current masthead page.

Reactions of Protonated 1,3-Diaza-4,4-diphenyl-2-(methylthio)butadienes with Isocyanides: Preparation of Imidazole and Triazine Derivatives

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Protonated 1,3-diazabutadienes **4** are prepared and treated with isocyanides. The reactions are much faster with salts **4** than with corresponding diazadienes **5**. The 5-iminoimidazolines **10** and **11**, which are the expected [1 + 4] cycloaddition products, are generally obtained. However, rearranged imidazoles **12** and **14** and 5-thioxoimidazolines **13** are predominantly formed in some cases. A mechanism is suggested to explain this rearrangement. A proton transfer from the more acidic salts **4** to isocyanides can also occur and the [2 + 4] cycloaddition reaction of resulting nitrilium salts with diazadienes **5** has been observed to give triazinium salts.

Cycloaddition reactions of heterodienes have been shown to be of great potential for synthesis in heterocyclic chemistry.[1-3] There are some literature reports concerning the participation of 1,3-diazabutadienes as 2π or 4π components in [2 + 2] or [2 + 4] cycloadditions.[2-5] However, examples of [1 + 4] cycloadditions of isocyanides with 1,3-diazabutadienes are rare and have not been exploited for the synthesis of heterocyclic compounds. Isocyanides easily react with 4,4-bis(trifluoromethyl)-1,3-diazabutadienes,[6,7] but these substances are not particularly representative for the parent system. Another reported reaction requires drastic conditions (only one example).[8]

Recently, we reported that the regioselective [1 + 4] cycloaddition of isocyanides with methyl 4,6-diaza-5-(methylthio)hepta-2,4,6-trienoates produces imidazoline derivatives in good yields.[9] We have now observed that the cycloaddition of isocyanides with 1,3-diaza-4,4-diphenyl-2-(methylthio)butadienes **5** proceeds more sluggishly. Therefore, we were attracted to the possibility that the rate of these reactions could be accelerated under acidic conditions.

It has been shown that Lewis acid catalysts can induce the [1 + 4] cycloaddition of isocyanides with α,β-unsaturated ketones[10,11] or *N*-acylimines.[12] Two examples of the protic acid catalyzed reaction of *tert*-butyl isocyanide with arylideneanilines have also been reported to give 3-amino-2-arylindoles.[13]

We have examined the reactivity of isocyanides **7–9** with protonated 1,3-diaza-2-(methylthio)(or *p*-tolylthio)butadienes **4** and found that most of these diazadiene salts **4** rapidly gave the [1 + 4] cycloaddition products. However, a proton transfer from **4** to isocyanides can also occur, and the [2 + 4] cycloaddition of resulting nitrilium salts with diazabutadienes **5** can be expected. The present paper describes the results of our investigations for elucidating the various reactions of protonated diazabutadienes **4** opposite to isocyanides.

Results and Discussion

Preparation of Diazabutadienes 5 and Their Salts 4. Two alternative procedures were used. The addition of diphenylmethylenamine (**1**) to isothiocyanates **2** yielded 3-aza-1-thiabutadienes **3**, which were alkylated with MeI to afford **4a–c**. In $CHCl_3$ solution containing an excess of triethylamine, **4a–c** led to diazadienes **5a–c**. Diazadienes **5e–h** were obtained by the reaction of **1** with imino chloro sulfides **6e–h**, in the presence of an excess of Et_3N. The treatment of a etheral solution of **5e–h** with dry HCl gave **4e–h** in good yields.

Reactions of Protonated Diazabutadienes 4 with Isocyanides 7–9. The reactions were carried out with an excess of isocyanide, in chloroform solution at room temperature (method A) or in refluxing acetonitrile (method B). Salts **4d,e** were also prepared and converted in situ by the treatment of corresponding diazadienes **5c,e** with pyridinium chloride and *tert*-butyl isocyanide in refluxing MeCN (method C).[14] The complexity of these reactions was revealed by considering the number of isolated products (Table I). On one hand, we observed some expected

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(14) In Table I, we have selected procedure A, B, or C in order to optimize the yields of resulting compounds. That choice did not induce any perturbation in the products distribution.

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