tomer with triflic anhydride without serious concomitant formation of aldol-type byproducts.

Experimental Section

General. All manipulations of compounds and solvents were carried out using standard Schlenk techniques. Solvents were degassed and purified by distillation under nitrogen from standard drying reagents. Spectroscopic measurements utilized the following instrumentation: ^{1}H NMR, Varian XL 300; ^{13}C NMR, Varian XL 300 (75.4 MHz); ^{19}F NMR, Varian XL 300 (282.2 MHz). NMR chemical shifts are reported in δ vs Me_4Si assigning the $CDCl_3$ resonance in ^{13}C spectra to be at 77.00 ppm; C_6D_6 resonance in ^{13}C spectra to be at 128.00 ppm. ^{19}F chemical shifts are reported in δ vs CF_3CO_2H at 76.53 ppm. Carbonyl compounds were purchased and used as follows; heptanal from Eastman Kodak and bulb-to-bulb transferred before use; 2-ethylbutyraldehyde from Aldrich, distilled before use; cyclohexanone from Matheson Coleman & Bell, distilled before use. Tf_2O was prepared from TfOH distilled from P_2O_5 and Celite. *Important*: The Tf_2O should be freshly (ca. within 2–3 days) distilled from P_2O_5 before use and stored under N_2 for the best and most consistent results.

General Method for Vinyl Triflate Preparations Using Polymer-Bound 2,6-Di-*tert*-butylpyridine (2). A small flask was charged with the appropriate solvent (14.5 mL), polymer-bound 2,6-di-*tert*-butylpyridine (4.9 mmol, 2.08 g), the corresponding aldehyde or ketone (4.7 mmol), and Tf_2O (4.75 mmol, 1.34 g). The reaction mixture was stirred at room temperature or refluxed depending on the system investigated. Upon the completion of the reaction the mixture was diluted with pentane (50 mL). The pentane solution was decanted from the polymer-bound base and washed with water (50 mL) and then brine (25 mL). The organic layer was filtered through basic alumina with pentane elution, and then the sovents were removed by rotary evaporation to yield the appropriate vinyl triflate. The polymer-bound base was regenerated for further use using previously published procedures.[7b]

Spectroscopic data for **5**: Assignments of stereochemistry were based upon the coupling pattern for the vinyl protons in the two isomers. (*Z*)-**5** isomer: ^{1}H NMR ($CDCl_3$) δ 6.48 (d, J = 5 Hz, =CHOTf, 1 H), 5.21 (dt, J = 5, 8 Hz, CH_2CH=, 1 H), 2.20–2.10 (m, CH_2CH=, 2 H), 1.40–1.00 (m, CH_2's, 6 H), 0.80 (t, J = 7 Hz, CH_3, 3 H); ^{13}C NMR ($CDCl_3$) δ 135.2 (=CHOTf), 120.9 (CH=), 118.6 (q, CF, J = 320 Hz), 31.2, 28.2, 24.1, 22.3 (CH_2's), 13.9 (CH_3). (*E*)-**5** isomer: ^{1}H NMR ($CDCl_3$) δ 6.44 (d, J = 12 Hz, =CHOTf, 1 H), 5.72 (dt, J = 12, 7 Hz, CH_2CH=, 1 H), 2.04–1.94 (m, CH_2CH=, 2 H), 1.40–1.00 (m, CH_2's, 6 H), 0.80 (t, J = 7 Hz, CH_3, 3 H); ^{13}C NMR ($CDCl_3$) δ 135.8 (=CHOTf), 122.9 (CH=), 31.0, 28.4, 26.5 (CH_2's), remaining signals overlapped with the *Z* isomer.

Relative Rate Experiments. Stock solutions were prepared by weighing out a calculated amount of solvent and reagent necessary to yield a 1.0 M stock solution of each reagent (i.e. carbonyl compound, base, and Tf_2O). The NMR tube was charged with the base solution 0.33 mL) and the appropriate aldehyde or ketone solution (0.33 mL). At this point NMR spectra were obtained to verify starting material purities and concentrations in the reaction mixture. Finally, the Tf_2O solution (0.33 mL) was added to the NMR tube to yield a reaction that was 0.33 M in each reactant. The progress of the reactions were then monitored by either ^{1}H, ^{13}C, or ^{19}F NMR techniques to obtain data on the reaction rates. Variable-temperature NMR spectra were collected in the temperature-controlled probe at the specified temperature. When reaction times exceeded 4 h the sample was placed in constant temperature bath in between collection of spectra. In the cases where the pyridinium salt was not in solution, usually when the reaction temperature was less than 40 °C, the NMR sample was centrifuged to move the solid to the top of the solution and out of the receiver coils in the probe to obtain maximum resolution.

Decomposition of *gem*-Bis(triflate) 4 in $CDCl_3$ and CCl_4. *gem*-Bis(triflate) was prepared following the procedure of Martinez and co-workers.[11] Stock solutions were prepared by weighing out a calculated amount of the appropriate solvent and *gem*-bis(triflate) with enough base (0.411 g) to yield a ~1.0 M stock solution. The NMR tubes were charged to give 0.5 M samples. ^{19}F NMR techniques were used to follow the decomposition of the *gem*-bis(triflate) in the appropriate solvent.

Acknowledgment. M.E.W. wishes to thank to the Office of the Vice President for Research at Utah State University for generously funding this research. We would also like to thank Prof. Jack Norton for sharing experimental results prior to publication.

Cephalosporins from Glycinic Esters. 1. Total Synthesis of the Cephamycin Framework†

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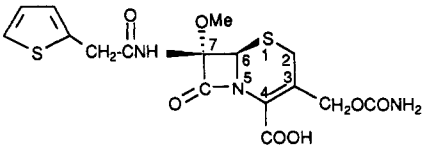
Received November 7, 1988

Δ^3 and Δ^2 N-protected 7-methoxycephem isomers are synthesized from thiazabutadiene derived from methoxyglycinate, in three major steps: hetero Diels–Alder cycloaddition, functional conversions, and lactamization.

During the past two decades, numerous semisynthetic cephalosporins have been prepared by varying the side chains at the 3- and 7-positions of 7-aminocephalosporinic acid or its analogues. These studies have generated compounds of broader antibacterial activity and improved pharmacokinetic properties.[1,2] Since the discovery of cefoxitin,[3] semisynthetic derivatives have been developed which benefit from the β-lactamase stability conferred by the 7-position α-methoxy functionality.



Cefoxitin

Here, we report a new and widely applicable total synthesis which affords Δ^3 or Δ^2 7-methoxy cephalosporin

† Dedicated to Emeritus Professor Noël Lozac'h on the occasion of his 73rd birthday.

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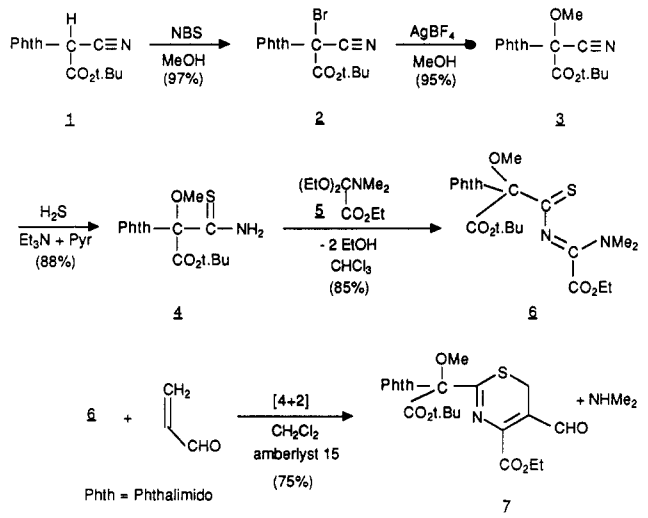
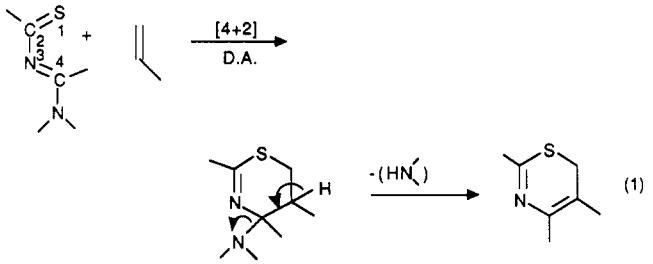
0022-3263/89/1954-2889$01.50/0

Scheme I



isomers bearing a protected amino group at the 7-position, as analogues of cephamycins. An advantage of this approach, compared to other methods,[2,3b] is in the introduction of the methoxy group at the beginning of the synthesis. Another important feature is the use of a versatile Diels–Alder reaction to form the cephalosporin nucleus.

In the last few years, 1-thia-3-aza-1,3-butadienes have been extensively investigated in our laboratory, as 4π components in Diels–Alder reactions (eq 1).[4-7]

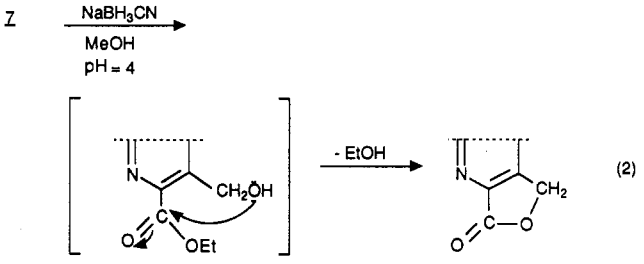


1,3-Thiazines are the key intermediates in multistep syntheses already carried out successfully on simpler models.[8-10] The strategy detailed here illustrates a more complex application. In particular, two examples show the possibility of converting the formyl group into other functionalities during the synthesis. Such a group is especially versatile for subsequent conversions. In addition, the efficiency of the synthesis makes these compounds particularly accessible as cephamycin precursors compared to the semisynthetic methods hitherto described.

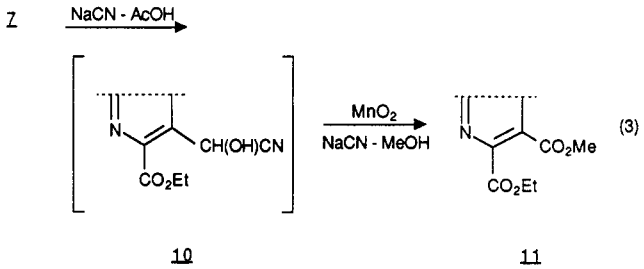
Results and Discussion

The 1-thia-3-aza diene **6** was obtained from *tert*-butyl α-methoxyglycinate, which had been prepared from *tert*-butyl 2-cyanophthaloylglycinate **1**[6] (Scheme I). Bromination using NBS, followed by the action of $AgBF_4$ in MeOH, afforded *tert*-butyl 2-cyano-2-methoxyglycinate **3** in excellent yield. Thioamide **4**, obtained after addition of H_2S to the nitrile function, reacted with orthoamide **5**[11,12] to give the required thiaza diene **6**. The best yields in cycloaddition reactions with thiaza diene **6** were obtained by using acrolein as dienophile and Amberlyst 15 as catalyst.[13] The intermediate cycloadduct was not isolated. Instead the desired thiazine **7** was formed by spontaneous elimination of a molecule of dimethylamine.

The next step of the synthesis required selective reduction of the imine double bond. Treatment of thiazine **7** with $NaBH_3CN$[14-16] afforded lactone **9**, resulting from the preferential reduction of the formyl group to the intermediate alcohol **8**, rather than the desired dihydrothiazine (eq 2).



This difficulty was overcome by transforming the formyl group into a function that is less readily reduced. The CHO → CO_2Me conversion was accomplished by treatment with NaCN + AcOH, followed by oxidation of the intermediate cyanohydrin **10** using MnO_2 in the presence of MeOH[17] (eq 3).



Attempts to obtain the functionalized 1,3-thiazine **11** directly by treatment with acrylate or acrylonitrile were unsuccessful. The [4 + 2] cycloaddition with these dienophiles does not proceed further than the intermediate

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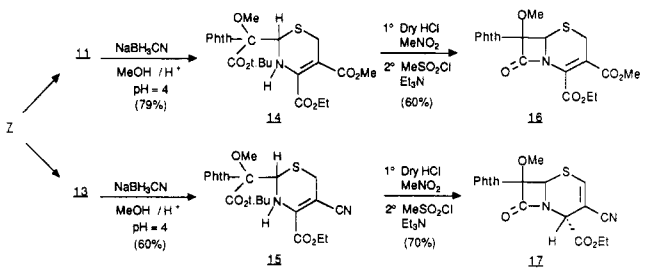
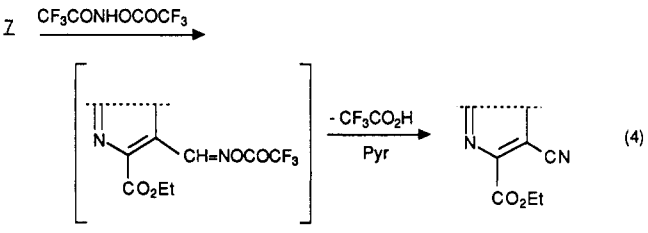
Scheme II



cycloadduct; elimination of the amine moiety does not occur spontaneously under the reaction conditions.

Conversion of **7** to cyano ester **13** was accomplished by treatment with *O,N*-bis(trifluoroacetyl)hydroxylamine[18] in pyridine (eq 4).



(4)

12 **13**

After conversion of the formyl group to the methyl ester or the nitrile, regioselective reduction of the C=N was possible. Treatment of thiazines **11** and **13** with excess $NaBH_3CN$ at pH = 4 gave, after purification by chromatography, one diastereomer of dihydrothiazines **14** and **15**, respectively (Scheme II).

Cleavage of the *tert*-butyl ester of thiazines **14** and **15** was achieved by using dry hydrogen chloride, affording the corresponding acids. The lactamization reaction was modeled after Watanabe's synthesis of monobactams.[19] This method, carried out earlier on simpler compounds,[20] proceeds in satisfactory yield by treatment with $MeSO_2Cl$ and Et_3N. Compound **14** gave one diastereomer of the Δ^3 cephem **16**. Dihydrothiazine **15**, on the other hand, afforded one diastereomer of the Δ^2 cephem **17**. In each case, it would appear that only one isomer (at C_7) was obtained from the lactamization reaction. Evidently only one isomer results from the iminium group reduction. Perhaps the bulky phthalimido group hinders the β-side of the heterocycle.

These results are consistent with those obtained in the 7-methyl cephalosporin series,[21] in which the $\Delta^3 \rightarrow \Delta^2$ cephem transposition, induced by triethylamine[1] present in the reaction mixture, is slow if R^3 is a methoxycarbonyl group and fast if R^3 is a nitrile group.

It is worth noting that, although isomerization to the Δ^2 cephem introduces a new chiral center, the cephem **17** is formed as a single diastereomer. It is probable, as suggested in the literature,[1] that during this reaction the bulky 4-ethoxycarbonyl group would be preferentially situated on the α side (exo) of the bicyclic structure.

Attempts were made to determine the stereochemistry about the C_6–C_7 bond by the nuclear Overhauser effect. In the 7-methoxycephem series, irradiation of the *O*-methyl group at the 7-position produced only a very slight increase in intensity[1,2,10,22] of the C-6 proton. We can therefore only very tentatively assign a configuration in which the OCH_3 group eclipses the hydrogen at position 6 in cephems **16** and **17**.

Conclusion

We have shown that is is possible to assemble the cephamycin framework from a disubstituted α-amino acid. The strategy employs a versatile Diels–Alder reaction, which should open the way to numerous structural variations. Presumably the ethyl ester at the 4-position could be replaced by a more readily cleavable ester (e.g., methyl ester hydrolyzable through enzymatic catalysis[23] or allyl ester deprotected via palladium catalysis[24,25]) and the protective phthaloyl group removed.[26–28] We hope to apply this synthetic approach to the construction of 7-methoxycephem derivatives suitable for conversion to useful cephamycin antibiotics.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded respectively on a Hitachi Perkin-Elmer instrument (R24B) and a JEOL instrument (J.N.M. FX 90M).

Thin-layer chromatography was performed on silica gel plates (0.25 mm, Merck). Column chromatography was carried out on silica gel (Merck Art. No. 7734, Kieselgel 60). All melting points were determined by using a microscope with a hot stage.

1,1-Dimethylethyl 2-(1,2-Benzenedicarboximido)-2-bromo-2-cyanoethanoate (2). A mixture of *tert*-butyl 2-cyano-2-phthalimidoethanoate[6] (2.86 g, 10 mmol) and NBS (1.96 g, 11 mmol) dissolved in anhydrous MeOH (60 mL) was stirred at room temperature for 30 min. After extraction with ethyl acetate, the organic layer was washed with brine, dried, filtered, and then concentrated under reduced pressure. The succinimide was removed by filtration through silica gel (elution CH_2Cl_2). Recrystallization of the residue from MeOH gave **2** as white crystals (3.39 g, 97%): mp 135–137 °C; IR (KBr) 1750, 1780, 1795 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.62 (s, 9 H), 7.97 (br s, 4 H); MS m/e = 291 ($M^{\bullet+}$ – 74). Anal. Calcd for $C_{15}H_{13}N_2O_4Br$: C, 49.33; H, 3.59; N, 7.67. Found: C, 49.36; H, 3.59; N, 7.78.

1,1-Dimethylethyl 2-(1,2-Benzenedicarboximido)-2-cyano-2-methoxyethanoate (3). A mixture of **2** (3.65 g, 10 mmol) and $AgBF_4$ (1.95 g, 10 mmol) in 100 mL of anhydrous MeOH was stirred under nitrogen for 72 h at room temperature. After filtration, the MeOH was evaporated and the residue dissolved in ethyl acetate. The solution was washed three times with brine, dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. Recrystallization of the residue from MeOH gave **3** (3 g, 95%): mp 143 °C; IR (KBr): 1750, 1775, 1795 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.59 (s, 9 H), 3.67 (s, 3 H), 7.92 (br s, 4 H); MS $M^{\bullet+}$ = 316. Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.49; H, 5.11; N, 8.19.

1,1-Dimethylethyl 2-(1,2-Benzenedicarboximido)-2-methoxy-2-thiocarbamoylethanoate (4). A stream of H_2S gas was passed through a solution of **3** (3.16 g, 10 mmol) in a 2:1 mixture of pyridine/triethylamine (40 mL) for 3 h. The solution was then degassed and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the resulting solution was washed with dilute HCl and then with water, dried (Na_2SO_4), and then concentrated. The crude solid was recrystallized from MeOH to give the thioamide **4** (3.08 g, 88%): mp 178–180 °C; IR (KBr) 1725, 1750, 1790 cm^{-1} (C=O), 2800, 2940, 3300 cm^{-1} (NH_2); ^1H

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NMR ($CDCl_3$) δ 1.50 (s, 9 H), 3.55 (s, 3 H), 7.85 (br s, 4 H), 8.35 (br s, 2 H); MS $M^{\bullet+}$ = 350. Anal. Calcd for $C_{16}H_{18}N_2O_5S$: C, 54.84; H, 5.18; N, 7.99. Found: C, 55.40; H, 5.04; N, 8.23.

6-(1,1-Dimethylethyl) 1-Ethyl 5-(1,2-Benzenedicarboximido)-2-(dimethylamino)-5-methoxy-4-thioxo-3-aza-2-hexenedioate (Thiaza Diene 6). A solution of thioamide **4** (1.75 g, 5 mmol) and orthoamide **5** (1.2 g, 5.5 mmol) in anhydrous $CHCl_3$ (50 mL) was refluxed for 24 h. The solution was concentrated, and the residue was chromatographed on silica gel. Elution with an ethyl acetate/petroleum ether mixture (70/30) gave a yellow oil. Crystallization from a mixture of ethyl acetate/petroleum ether gave **6** as yellow crystals (2.02 g, 85%): mp 185–187 °C; IR (KBr) 1730, 1760, 1780 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 3 H), 1.52 (s, 9 H), 3.33 and 3.36 (2 s, 6 H), 3.53 (s, 3 H), 4.34 (q, J = 7.2 Hz, 2 H), 7.82 (br s, 4 H); MS $M^{\bullet+}$ = 477. Anal. Calcd for $C_{22}H_{27}N_3O_7S$: C, 55.33; H, 5.70; N, 8.80. Found: C, 55.07; H, 5.69; N, 8.95.

1,1-Dimethylethyl 2-(1,2-Benzenedicarboximido)-2-[4-(ethoxycarbonyl)-5-formyl-6*H*-1,3-thiazin-2-yl]-2-methoxyethanoate (7). A solution containing thiaza diene **6** (0.95 g, 2 mmol), acrolein (3 mL), Amberlyst 15 (1.4 g), and a pinch (about 20 mg) of hydroquinone in CH_2Cl_2 (50 mL) was stirred for 2 h at room temperature. A further 3 mL of acrolein was added, and stirring was continued for several hours. Completion of the reaction was determined by TLC. The solution was then filtered and chromatographed on silica gel (elution with ethyl acetate/petroleum ether, 50/50). Crystallization from MeOH gave **7** as yellow crystals (0.72 g, 75%): mp 117 °C; IR (KBr) 1695, 1745, 1795 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.5 Hz, 3 H), 1.55 (s, 9 H), 3.37 and 3.99 (2 d, J = 15.2 Hz, 2 H, SCH_2), 3.62 (s, 3 H, OCH_3) 4.19 (q, J = 7.5 Hz, 2 H), 7.84 (br s, 4 H), 10.27 (s, 1 H, CHO); MS $M^{\bullet+}$ = 488. Anal. Calcd for $C_{23}H_{24}N_2O_8S$: C, 56.55; H, 4.95; N, 5.73. Found: C, 56.12; H, 4.94; N, 5.57.

1,1-Dimethylethyl 2-(1,2-Benzenedicarboximido)-2-[4-(ethoxycarbonyl)-5-(methoxycarbonyl)-6*H*-1,3-thiazin-2-yl]-2-methoxyethanoate (11). To a stirred solution of the aldehyde **7** (1.29 g, 2.64 mmol) and acetic acid (0.6 mL, 10.56 mmol) in MeOH (30 mL) was added NaCN (0.65 g, 13.2 mmol), followed by MnO_2 (4.6 g, 52.8 mmol). The resulting mixture was stirred for 1 h at room temperature. Ethyl acetate (40 mL) was then added, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with brine, concentrated, and chromatographed on silica gel (elution with ethyl acetate/petroleum ether, 50/50). Crystallization from MeOH gave the thiazine **11** (1.1 g, 80%): mp 120 °C; IR (KBr) 1600, 1735, 1790 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3 H), 1.53 (s, 9 H), 3.96 and 3.43 (2 d, J = 16 Hz, 2 H, SCH_2), 3.61 (s, 3 H, OCH_3), 3.81 (s, 3 H, CO_2CH_3), 4.16 (q, J = 7.5 Hz, 2 H), 7.85 (br s, 4 H); MS $M^{\bullet+}$ = 518. Anal. Calcd for $C_{24}H_{26}N_2O_9S$: C, 55.59; H, 5.05; N, 5.40. Found: C, 55.15; H, 5.11; N, 5.76.

1,1-Dimethylethyl 2-(1,2-Benzenedicarboximido)-2-[5-cyano-4-(ethoxycarbonyl)-6*H*-1,3-thiazin-2-yl]-2-methoxyethanoate (13). To a solution of aldehyde **7** (1.95 g, 4 mmol) in anhydrous C_6H_6 (8 mL) was added pyridine (0.78 mL, 9.6 mmol) followed by *O,N*-bis(trifluoroacetyl)hydroxylamine (1.08 g, 4.8 mmol). The mixture was refluxed for 2 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and chromatographed on silica gel. Elution with a mixture of CH_2Cl_2/ethyl acetate (95/5) gave a yellow oil (1.86 g, 96%): ^1H NMR ($CDCl_3$) δ 1.15 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.54 (s, 9 H, *t*-Bu), 3.60 (s, 3 H, OCH_3), 3.42 and 3.90 (2 d, J = 16.2 Hz, 2 H, SCH_2), 4.20 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 7.84 (br s, 4 H, Phth); MS m/e = 385 ($M^{\bullet+}$ – 100). Anal. Calcd for $C_{23}H_{23}N_3O_7S$: C, 56.89; H, 4.77; N. 8.66. Found: C, 56.72; H, 4.52; N, 8.51.

1,1-Dimethylethyl 2-(1,2-Benzenedicarboximido)-2-[4-(ethoxycarbonyl)-5-(methoxycarbonyl)-3,6-dihydro-2*H*-1,3-thiazin-2-yl]-2-methoxyethanoate (14). To a sitrred solution of thiazine **11** (0.50 g, 0.96 mmol) in MeOH (20 mL), in the presence of bromocresol green, was added $NaBH_3CN$ (60 mg, 0.96 mmol) at room temperature. The pH was maintained by successive additions of 2 N HCl in MeOH. The addition of 60 mg of $NaBH_3CN$ was repeated as often as necessary until total reduction of the thiazine as monitored by TLC (ethyl acetate/petroleum ether, 50/50). The mixture was saturated with NaCl and extracted with ethyl acetate. The resulting solution was dried, concentrated, and chromatographed on silica gel. Elution with a mixture of C_6H_6/ethyl acetate (95/5) gave the crude product. Recrystallization from MeOH gave the dihydrothiazine **14** (0.40 g, 79%): mp 154 °C; IR (KBr) 1620, 1735, 1790 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.57 (s, 9 H, *t*-Bu), 3.48 (s, 3 H, OCH_3), 3.69 (s, 3 H, CO_2CH_3), 3.51 and 3.83 (2 d, J = 16.6 Hz, 2 H, SCH_2), 4.26 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 5.55 and 5.65 (2 d, J = 5.4 Hz, 2 H, CHNH), 7.84 (br s, 4 H, Phth); MS $M^{\bullet+}$ = 520. Anal. Calcd for $C_{24}H_{28}N_2O_9S$: C, 55.37; H, 5.42; N, 5.38. Found: C, 55.11; H, 5.59; N, 5.53.

1,1-Dimethylethyl 2-(1,2-Benzenedicarboximido)-2-[5-cyano-4-(ethoxycarbonyl)-3,6-dihydro-2*H*-1,3-thiazin-2-yl]-2-methoxyethanoate (15). The procedure is identical with that described previously. One diastereomer was isolated (60%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.58 (s, 9 H, *t*-Bu), 3.48 (s, 3 H, OCH_3), 3.42 and 3.85 (2 d, J = 16.4 Hz, 2 H, SCH_2), 4.40 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 5.47 (d, J = 5.4 Hz, 1 H, CH), 6.70 (d, J = 5.4 Hz, 1 H, NH), 7.85 (br s, 4 H, Phth); MS $M^{\bullet+}$ = 487. Anal. Calcd for $C_{23}H_{25}N_3O_7S$: C, 56.66; H, 5.17; N, 8.62. Found: C, 56.49; H, 5.30; N, 8.48.

General Procedure for the Cleavage of *tert*-Butyl Dihydrothiazine Esters 14 and 15. A stream of dry HCl gas was passed through a solution of dihydrothiazine **14** (or **15**) (2 mmol) in CH_3NO_2 (40 mL) at 0 °C until saturation. The reaction mixture was stirred for 3 h at 0 °C and then concentrated under reduced pressure. The acid obtained was used directly in the next step.

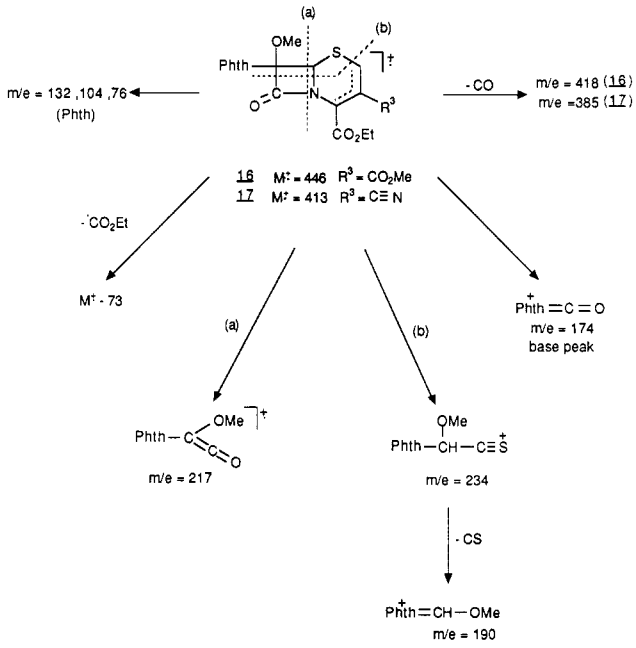
General Procedure for the Lactamization. To a solution of the acid (2 mmol) in anhydrous $CHCl_3$ (20 mL) were added tetrabutylammonium hydrogen sulfate (0.1 mmol), CH_3SO_2Cl (3 mmol), and Et_3N (6.3 mmol). The reaction mixture was stirred for 15 min at room temperature, then concentrated under reduced pressure, and chromatographed (elution with CH_2Cl_2/ethyl acetate, 95/5).

Δ^3-7-Methoxycephem 16: foam (0.53 g, 60%); IR (CCl_4) 1750, 1790, 1810 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 3.65 (s, 3 H, OCH_3), 3.80 (s, 3 H, CO_2CH_3), 3.39 and 4.05 (2 d, J = 17.5 Hz, 2 H, SCH_2), 4.41 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 5.30 (s, 1 H, CH), 7.90 (br s, 4 H, Phth); MS $M^{\bullet+}$ = 446. Anal. Calcd for $C_{20}H_{18}N_2O_8S$: C, 53.80; H, 4.06; N, 6.28. Found: C, 53.65; H, 3.99; N, 6.13.

Δ^2-7-Methoxycephem 17: oil (0.58 g, 70%); IR (CCl_4) 1755, 1790, 1810 (C=O); ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 3.61 (s, 3 H, OCH_3), 4.24 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 5.12 (d, J = 1.36 Hz, 1 H, H^4), 5.51 (s, 1 H, H^6), 7.37 (d, J = 1.36 Hz, 1 H, H^2), 7.88 (br s, 4 H, Phth); MS $M^{\bullet+}$ = 413. Anal. Calcd for $C_{19}H_{15}N_3O_6S$: C, 55.20; H, 3.66; N, 10.17. Found: C, 55.03; H, 3.72; N, 10.25.

MS fragmentation schemes for the Δ^2 and Δ^3 cephems are

Scheme III



identical and characteristic; they are consistent with those given in the literature for cephalosporins or 7-methoxycephalosporins.[1,3a,22] Note, in particular, loss of the lactam CO and fission along paths a and b in Scheme III.

Registry No. 1, 61934-81-4; 2, 119788-90-8; 3, 119788-91-9; 4, 119788-92-0; 5, 34644-30-9; 6, 119788-93-1; 7, 119788-94-2; 11, 119788-95-3; 13, 119788-96-4; 14, 119788-97-5; 15, 119788-98-6; 16, 119788-99-7; 17, 119789-00-3; acrolein, 107-02-8.

Model Studies Probing the Amino-Claisen Rearrangement Approach to Hydroisoquinoline Synthesis. Development of Methods for Stereocontrolled Introduction of Reserpine E Ring Type Functionality

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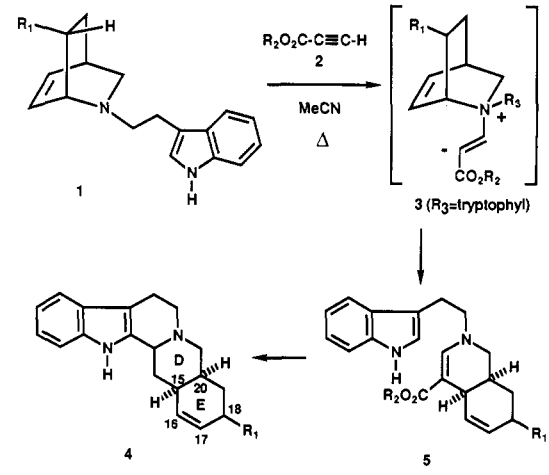
Received December 30, 1988

Studies probing several aspects of a proposed yohimbane alkaloid synthetic strategy based upon the zwitterionic amino-Claisen rearrangement reactions of isoquinuclidenes have been conducted. As part of these efforts, methods have been developed to prepare 7-ketoisoquinuclidenes and their derivatives. An approach to these substances utilizing an oxidative cleavage sequence starting with 7-acetylisoquinuclidenes has been shown to be limited to C-6 electron withdrawing group substituted systems owing to an interesting rearrangement reaction which occurs upon attempts to α-oxidize enolate anions derived from these substrates. A more successful approach has been developed which employs Diels–Alder cycloaddition of the ketene equivalent, α-acetoxyacrylonitrile to *N*-carbethoxy-1,2-dihydropyridine followed by deprotection to liberate the 7-ketone function. Zwitterionic amino-Claisen rearrangements occurring in reactions of a series of isoquinuclidenes with alkyl propiolates have been probed, and limitations of this process have been uncovered. However, the diethoxy ketal of a 7-ketoisoquinuclidene has been shown to be efficiently converted to an enone-containing, cis-fused hydroisoquinoline upon treatment with methyl propiolate. Finally, methods for stereoselective introduction of the reserpine E ring functionality have been modeled. The strategy involves cyanosilylation of the enone function followed by hydroboration–oxidation of the regioselectively formed silyl enol ether, alcohol methylation, silyl ether deprotection, and esterification. The stereochemical aspects of these processes are discussed.

In previous reports[1] we have described an efficient approach for yohimbane ring construction based upon a combination of zwitterionic amino-Claisen rearrangement and Wenkert cyclization methodologies. The strategy, outlined in Scheme I, utilizes rearrangement of the zwitterion **3** generated by conjugate addition of isoquinuclidenes **1** to propiolate esters **2**, to produce *N*-tryptophyl-*cis*-hydroisoquinolines **5**. (In this paper, tryptophyl is 2-indol-3-ylethyl.) These substances then undergo decarboxylative cyclization[2] to form the pentacyclic cis-D,E yohimbanes **4**. Since the isoquinuclidenes can be conveniently accessed by 1,2-dihydropyridine Diels–Alder routes, the overall process represents an efficient strategy for preparation of the structurally complex yohimbane members.

Application of this strategy to the synthesis of interesting members of the yohimbane family requires the development of methods for stereocontrolled introduction of E-ring functionality that is commonly found in these substances. Reserpine (**10**) with its differentially functionalized *trans*-diol groups at C-17 and C-18 and β-methoxycarbonyl group at C-16 of the DE-cis-fused pentacyclic skeleton represents the perhaps most challenging of the targets in this area from the viewpoint of functionality and stereochemistry complexity. As a result of this, we have further probed our strategy for yohimbane

Scheme I



synthesis with the intent of demonstrating its compatibility with procedures for stereoselective introduction of the reserpine E ring functionality. Our plan, outlined in Scheme II, was to utilize the enone-containing cis-fused hydroisoquinoline **7** as a key intermediate. The ester function at C-16 would be introduced in the form of a cyano group by silyl-cyanation chemistry. Hydroboration of the resulting silyl enol ether **8** would then furnish the regioselectively blocked, vicinal diol **9**, which we felt would serve as a useful precursor of the target alkaloid. Conformational considerations (see below) suggested that the chiral centers introduced by these operations would be delivered with the desired relative stereochemistry. In

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(2) (a) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461. (b) Wenkert, E.; Spague, P. W.; Webb, R. L. *J. Org. Chem.* **1973**, *38*, 4305.

0022-3263/89/1954-2893$01.50/0