stereoelectronically acceptable, but models show that it has a severe nonbonded interaction between the Lewis acid and H_c. The other cyclizations shown in the table can be similarly rationalized. We are continuing our investigations in this area.

Acknowledgment. We are grateful to the National Cancer Institute (CA-34303) for support of this research, to A Freyer for NMR spectra, and to Dr. R. Minard for mass spectra.

Registry No. 1, 93455-37-9; 2, 102918-85-4; 3, 102853-10-1; 4, 102853-11-2; 5, 102853-12-3; 6, 102853-13-4; 7, 102853-14-5; 8, 102853-15-6; 9, 102853-16-7; 10, 102853-17-8; 11, 102918-86-5; 12, 102853-18-9; 13, 102918-87-6; 14, 102853-19-0; 15, 102869-93-2; 16, 102853-20-3.

Supplementary Material Available: X-ray data on Diels-Alder adduct 10 (9 pages). Ordering information is given on any current masthead page.

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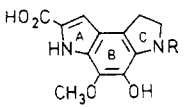
Diels-Alder Reactions of Heterocyclic Azadienes: Total Synthesis of PDE-II Methyl Ester

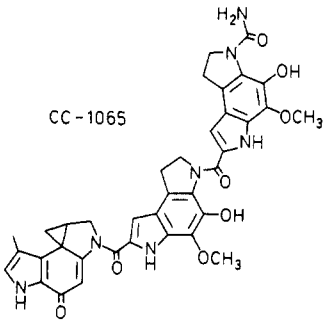
Summary: The total synthesis of the methyl ester of PDE-II (**2**), a 3',5'-c-AMP phosphodiesterase inhibitor constituting the central and right-hand 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole segment of the potent antitumor-antibiotic CC-1065, is described and is based on the utilization of two heterocyclic azadiene Diels-Alder reactions: an inverse electron demand Diels-Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate and a subsequent intramolecular Diels-Alder reaction of an alkyne 1,2-diazine.

Sir: PDE-I (**1**) and PDE-II (**2**), two potent 3',5'-c-AMP phosphodiesterase inhibitors isolated from *Streptomyces* strain MD769-C6[1] whose structures were identified by



R = $CONH_2$ 1
R = $COCH_3$ 2

single-crystal X-ray structural analysis[2] and subsequently confirmed by total synthesis,[3,4] possess the identical 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole skeleton composing the central and right-hand segments of CC-1065 (**3**), a potent antitumor-antibiotic isolated from *Streptomyces zelensis*.[5,6] Herein we detail our initial efforts on the total



3

synthesis of CC-1065 which have resulted in the total synthesis of PDE-II methyl ester (**25**) and which are based on the implementation of two heterocyclic azadiene Diels-Alder reactions: the inverse electron demand Diels-Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate and a subsequent intramolecular Diels-Alder reaction of an alkyne 1,2-diazine.

Reaction of 4,4-dimethoxybut-3-en-2-one (**5**)[7] with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**4**)[8] in refluxing dioxane provided the dimethyl 1,2-diazine-3,6-dicarboxylate (**6**) (71%, Scheme I).[9] Reduction of the methyl ketone of **6** with sodium borohydride (THF, 10 equiv of H_2O, -23 °C, 82%) afforded the lactone **7**[10] and provided an effective differentiation of the two methoxycarbonyl groups. The remaining C-3 methyl ester was removed by hydrolysis and an unexpectedly facile decarboxylation of the resultant carboxylic acid. Treatment of **7** with 2.1 equiv of lithium hydroxide (THF/MeOH/H_2O, 23 °C, 1 h) followed by acidification and extended exposure of **8** to aqueous acid (23 °C, 4 h) provided **9** in 82% recrystallized yield. The room temperature, acid-catalyzed decarboxylation of **8**, as monitored by the slow evolution of gas, proceeded more effectively than anticipated or precedented in related work.[11]

Treatment of the lactone **9** with ammonia (MeOH, 23 °C, 1 h) provided the unstable hydroxy amide **10** which was immediately protected as the *tert*-butyldimethylsilyl (TBDMS) ether,[12] affording the amide **11** as a stable, crystalline solid. Subjecting **11** to a modified Hofmann

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(2) Nakamura, H.; Enomoto, Y.; Takeuchi, T.; Umezawa, H.; Iitaka, Y. *Agric. Biol. Chem.* **1978**, *42*, 1337.
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(10) All stable compounds were characterized by ^1H NMR (^{13}C NMR), IR, EI/CIMS, and gave satisfactory C,H,N analyses or exact mass (HRMS) determinations.
(11) 1,2-Diazine-3-carboxylic acids generally require temperatures in excess of 200 °C in order to promote decarboxylation.[9] However, room temperature decarboxylation of the C-3 carboxylate of 4-alkoxy-1,2-diazine-3-carboxylic acids including **8** appears to be general: Boger, D. L.; Coleman, R. S.; Patel, M., unpublished observations.
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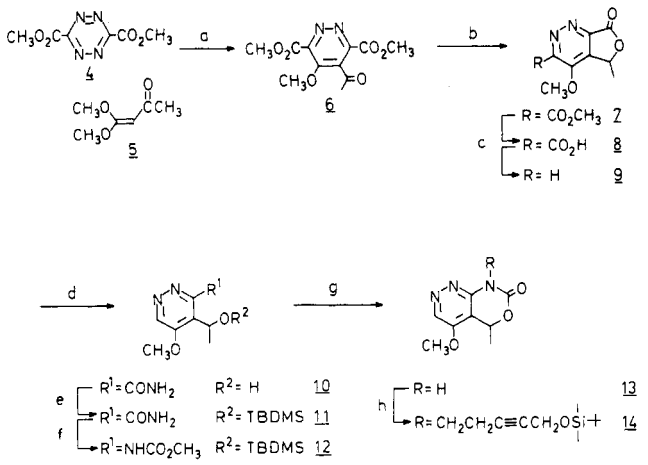
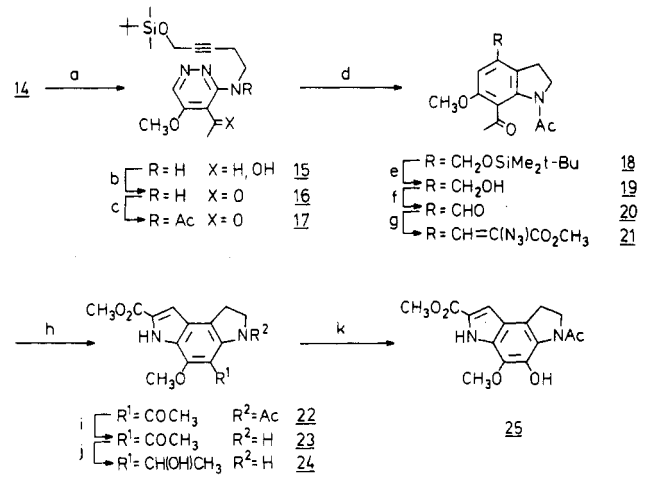
0022-3263/86/1951-3250$01.50/0

Scheme I[a]



[a] (a) 1.5 equiv of **5**, 0.25 M in dioxane, 101 °C; 3 h, 71%; (b) 1.1 equiv of $NaBH_4$, THF, 10 equiv of H_2O, −23 °C, 1 h, 82%; (c) 2.1 equiv of LiOH, THF/MeOH/H_2O (3:1:1), 25 °C, 1 h; HCl, pH 1, 4 h, 25 °C, 82% from **7**; (d) NH_3, MeOH, 25°C, 1 h; (e) *t*-$BuMe_2SiCl$, imidazole, DMF, 25 °C, 63% (28% recovered **9**); (f) 1.25 equiv of MeOBr, 4 equiv of NaOMe, MeOH, −43 to 0 °C, 30 min; 60 °C, 30 min; (g) H_2SO_4, H_2O, pH 1, 12 h, 25 °C, 82% from **11**; (h) 1.4 equiv of 5-((*tert*-butyldimethylsilyl)oxy)-3-pentyn-1-ol, 1.4 equiv of Ph_3P, 1.4 equiv of diethyl azodicarboxylate, THF, 22 °C, 18–24 h, 61%.

Scheme II[a]



[a] (a) 2 equiv of KOH, 6 equiv of *t*-BuOK, ether, 0 °C, 15 min; (b) 10 wt equiv of MnO_2, CH_2Cl_2, 22 °C, 24–36 h, 66–79% from **14**; (c) neat Ac_2O, 10 equiv of NaOAc, 120 °C, 90 min, 90%; (d) 230 °C, 0.05 M in 1,3,5-triisopropylbenzene, argon, 18 h, 82%; (e) AcOH/THF/H_2O (3:1:1), 22 °C, 12–18 h; (f) 10 wt equiv of MnO_2, CH_2Cl_2, 22 °C, 18 h, 74% from **18**; (g) 10 equiv of $N_3CH_2CO_2CH_3$, 8 equiv of NaOMe, MeOH, −23 to 0 °C, 1 h; (h) xylene, 0.05 M, N_2, reflux, 2.5 h, 56% from **20**; (i) anhydrous HCl, MeOH, 70 °C, 12 h, 85%; (j) excess $NaBH_4$, MeOH, 22 °C, 15 min, 78%; (k) 5 equiv of H_2O_2, 10 equiv of BF_3 etherate, CH_2Cl_2, 22 °C, 1 h; 10 equiv of Ac_2O, NaOAc, THF, 22 °C, 4 h.

rearrangement[13] (MeOBr, NaOMe, MeOH, −43 °C to 0 °C, 30 min; 60 °C, 30 min) afforded the labile methyl carbamate **12**. Acid-catalyzed deprotection of **12** and subsequent cyclization of the free alcohol provided **13** in 82% overall yield from **11**. Introduction of an alkyne-bearing side chain was achieved by Mitsunobu alkylation[14] of **13** with 5-((*tert*-butyldimethylsilyl)oxy)-3-pentyn-1-ol affording **14** (61%)[15] and completed the assemblage of the necessary components for an intramolecular 1,2-diazine Diels–Alder construction of the BC indoline ring system of PDE-II.[16]

Hydrolysis[17] of **14** (anhydrous KOH, potassium *tert*-butoxide, ether, 0 °C, 15 min, Scheme II) provided the unstable amino alcohol **15**, which was oxidized directly to the amino ketone **16** (MnO_2, CH_2Cl_2, 22 °C, 24 h, 66–79% overall from **14**). Subsequent N-acetylation (neat Ac_2O, 10 equiv of NaOAc, 120 °C, 90 min) afforded amide **17** (90%). Intramolecular Diels–Alder cycloaddition[16] of **17** in 1,3,5-triisopropylbenzene (230 °C, 18 h) in a sealed vessel under argon provided an 82% isolated yield of indoline **18** and completed the construction of the indoline BC-ring system of PDE-II.

Introduction of the A ring of PDE-II was achieved by using the methodology of Hemetsberger and Rees[18] (Scheme II). Deprotection[12] of the *tert*-butyldimethylsilyl ether of **18** (AcOH/THF/H_2O, 22 °C, 18 h) followed by oxidation of the resultant alcohol **19** (MnO_2, CH_2Cl_2, 22 °C, 18 h) afforded indoline-4-carboxaldehyde **20** (74% overall from **18**). Condensation of **20** with methyl azidoacetate (NaOMe, MeOH, 0 °C, 1 h) provided the unstable styryl azide **21**, which cyclized upon thermolysis (xylene, reflux, N_2, 2.5 h) affording **22** in 56% overall yield from **20**. This intramolecular pyrrole-2-carboxylate formation proved to be an excellent procedure for introduction of the sixth substituent of the hexasubstituted B-ring of PDE-II and served to complete the construction of the 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole skeleton.[4,16]

Removal of the *N*-acetyl group of **22** (anhydrous HCl, MeOH, 70 °C, 12 h) gave the amino ketone **23** (85%), which was reduced with sodium borohydride (MeOH, 22 °C, 15 min) to afford the secondary benzylic alcohol **24** (78%). The phenolic hydroxyl was introduced by using a benzylic hydroperoxide rearrangement[19] of **24**. Treatment of **24** with hydrogen peroxide and boron trifluoride etherate[20] (CH_2Cl_2, 22 °C, 1 h) followed by immediate acetylation of crude amino phenol (Ac_2O, NaOAc, THF, 22 °C, 4 h) provided PDE-II methyl ester (**25**), identical in all comparable respects (^1H NMR, IR, EIMS, HRMS, TLC) with the methyl ester of authentic PDE-II.[21] This late, apparently indirect, introduction of the C-4 hydroxyl group permits the effective differentiation of the PDE-I/II B-ring oxygen substituents and avoids the anticipated instability of intermediates bearing a readily oxidized free phenol.[22]

(13) Radlick, P.; Brown, L. R. *Synthesis* **1974**, 290.
(14) Mitsunobu, O. *Synthesis* **1981**, *1*.
(15) 1,2-Diazine N-2-alkylated material was isolated in 35% yield.[16]

(16) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240.
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(20) For use of this reagent in Baeyer–Villiger oxidations of aliphatic ketones, see: McClure, J. D.; Williams, P. H. *J. Org. Chem.* **1962**, *27*, 24.
(21) Comparison was based on published[1] spectral data, copies of ^1H NMR and IR spectra supplied by H. Umezawa, and by direct comparison of ^1H NMR ($CDCl_3$, 200 MHz) and SiO_2 TLC (2.5% CH_3OH–$CHCl_3$, EtOAc, 80% EtOAc–hexane, Et_2O solvent systems) with PDE-II methyl ester prepared by CH_2N_2 esterification[1] of a sample of PDE-II generously provided by C. W. Rees.
(22) A full discussion of this and related observations will be detailed in a full account of this and related studies.
(23) (a) National Institutes of Health research career development award recipient, 1983–88 (CA 00898/01134). Searle Scholar recipient, 1981–85. Alfred P. Sloan research fellowship recipient, 1985–89. (b) National Institutes of Health predoctoral trainee, 1984–85 (GM 07775). David Ross Fellow, Purdue University, 1986–1987. (c) The initial stages of this work were conducted within the Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045.

The extension of this work to the preparation of the left-hand segment of CC-1065 and the incorporation of the monomer units into the total synthesis of CC-1065 are in progress.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA 41986), the Searle Scholars Foundation, and the Alfred P. Sloan Foundation. We thank Professor H. Umezawa for providing copies of the ^{1}H NMR and IR spectra of natural PDE-II and PDE-II methyl ester and Professor Charles W. Rees for providing a sample of synthetic PDE-II.

Registry No. 4, 2166-14-5; 5, 50473-61-5; 6, 92144-09-7; 7, 103150-48-7; 8, 103150-49-8; 9, 103150-50-1; 10, 103150-51-2; 11, 103150-52-3; 12, 103150-53-4; 13, 103150-54-5; 14, 103150-55-6; 15, 103150-56-7; 16, 103150-57-8; 17, 103150-58-9; 18, 103150-59-0; 19, 103150-60-3; 20, 103150-61-4; 21, 103150-62-5; 22, 103150-63-6; 23, 103150-64-7; 24, 103150-65-8; 25, 67805-50-9; 25 (deacetylated), 103150-66-9.

Supplementary Material Available: Full spectral and physical characterizations of 6–25 are provided (6 pages). Ordering information may be found on any current masthead page.

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Additions and Corrections

Vol. 44, 1979

C. H. Heathcock,* M. C. Pirrung, and J. E. Sohn. Acyclic Stereoselection. 4. Assignment of Stereostructure to β-Hydroxycarbonyl Compounds by Carbon-13 Nuclear Magnetic Resonance.

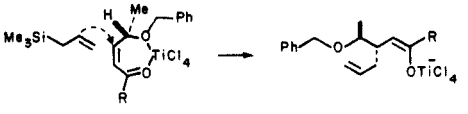
Page 4295. Entry 25 in Table I is incorrect and should be replaced by

25	*t*-Bu	OMe	78.1	12.8	41.1	82.5	17.9	38.6

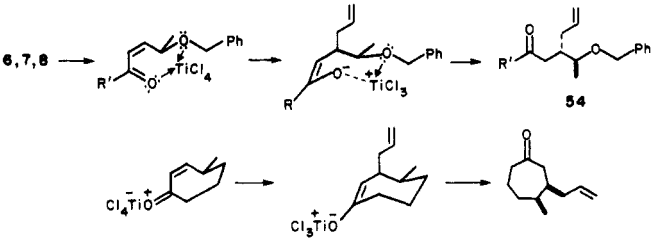
Vol. 49, 1984

Clayton H. Heathcock,* Syun-ichi Kyooka, and Todd A. Blumenkopf. Acyclic Stereoselection. 22. Diastereofacial Selectivity in the Lewis Acid Mediated Reactions of Allylsilanes with Chiral Aldehydes and Enones.

Page 4218. The unnumbered equation at the lower left of the page should be replaced by



If one assumes that the seven-membered chelate resembles a cycloheptanone with the methyl substituent "equatorial", the topography of the reaction is similar to that observed for 4-methylcycloheptenone: Blumenkopf, T. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2354.



Vol. 50, 1985

Kazuhiko Takai and Clayton H. Heathcock*. Acyclic Stereoselection. 32. Synthesis and Characterization of the Diastereomeric (4*S*)-Pentane-1,2,3,4-tetrols.

Page 3248. The conformations depicted for the side chains in compounds **10** and **12** in Chart I are not consistent with the observed coupling constants between H_a and H_b (Table II). Correct conformations for **10** and **12** are given below:

Chart I