the corresponding cyano cuprate (Scheme II) to 2-carbomethoxy-4,4-dimethyl-2-cyclopenten-1-one[7] **6** (85%). The resulting keto ester **7**[8] was subjected to K_2CO_3 (1.5 equiv) and *N*-phenyltrifluoromethanesulfonimide[9] (1.5 equiv) in refluxing DME to provide the β-enol triflate **8** (83%). The key methallyl appendage was easily introduced to this compound by reaction of β-enol triflate **8** with methallyl cuprate[10,11] (1.5 equiv, THF, -24 °C, 3 h) to produce the β-substituted unsaturated ester **9** in excellent yield (96%). Reduction of the conjugated ester **9** to the allylic alcohol (LAH, 0 °C) and hydrolysis of the OBO ortho ester functionality (HCl, THF, 1 min, 25 °C) and subsequent saponification (3 M KOH, MeOH, 3 h) resulted in the procurement of hydroxy acid **10** (86%). We were pleased to discover that the lactonization of hydroxy acid **10** under high dilution conditions (0.005 M) using Mukaiyama's salt[12] (2-chloro-*N*-methylpyridinium iodide, NEt_3) in refluxing acetonitrile afforded lactone **5** (mp 72-73 °C) in good yield (79%).

Having completed the preparation of the key intermediate, we were anxious to investigate the rearrangement of lactone **5** to silyl ester **3**. Examination of molecular models seemed to indicate that the chairlike transition state for rearrangement would be somewhat strained relative to the boatlike transition states in our previously examined systems[1] and, therefore, necessitate the isolation and subsequent thermolysis of ketene acetal **4**. Consequently, we were surprised to observe that the ketene acetal **4** derived from lactone **5** [$LiN(SiMe_3)_2$, 1.3 equiv, ClSi-*t*-$BuMe_2$, -78 → 25 °C] rearranged at or below room temperature to provide ester **3** (R = $SiMe_2$-*t*-Bu), which upon hydrolysis (HCl, H_2O, THF) gave acid **3** (R = H, mp 108-109 °C) in 79% overall yield.

All that remained to complete the formal total synthesis was the seemingly routine oxidation of the olefinic functionality present in acid **3**. Although the acyclic olefin of acid **3** smoothly underwent oxidative cleavage upon subjection to ozone (O_3, MeOH), the exocyclic olefin afforded the corresponding epoxide. This is not an uncommon occurrence in the ozonations of hindered olefinic systems,[13] e.g. longifolene.[14] Fortunately, ruthenium tetraoxide oxidation of diolefinic acid **3** using the procedure of Sharpless ($RuCl_3 \cdot (H_2O)_n$, $NaIO_4$, CCl_4, CH_3CN, H_2O)[15] gave diketo acid **2** (53%), identical in all respects (IR, NMR, MS, TLC, mp) with a sample kindly provided by Professor Schlessinger.

In summary, the preparation of bridged bicycloalkanes by alicyclic Claisen rearrangement is certainly feasible, and, in this particular example, it facilitated a stereospecific, 13-step, total synthesis of quadrone from carbomethoxy enone **6**. Further development and exploitation of this approach in organic synthesis is currently in progress.

Acknowledgment. We appreciate the financial and material support provided by the National Institutes of Health (Grant GM28663) and Eli Lilly and Company. High-field (360-MHz) ^1H and ^{13}C NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (Grant CHE-80-24328). Mass spectra were obtained through the National Science Foundation Regional Mass Spectroscopy Center at the University of Nebraska (Grant CHE-82-11164). We also thank Professor Schlessinger for providing spectra and a sample of diketo acid **2**.

Registry No. **1**, 102849-98-9; **2**, 102849-15-0; **3**, 102745-26-6; **4**, 102745-27-7; **5**, 102745-28-8; **6**, 86576-36-5; **7**, 102745-29-9; **8**, 102745-30-2; **9**, 102745-31-3; **10**, 102745-32-4; Tf_2NPh, 102745-33-5; quardrone, 66550-08-1; 2-chloro-1-methylpyridinium iodide, 14338-32-0.

Supplementary Material Available: Spectra and experimental details for compounds **2**, **3**, and **5**-**10** described in this paper (8 pages). Ordering information is given on any current masthead page.

[†]Alfred P. Sloan Foundation Fellow, 1985-1987.

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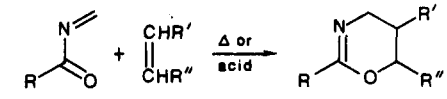
(5) For terminology, see: Corey, E. J.; De, B. *J. Am. Chem. Soc.* **1984**, *106*, 2735.
(6) For the preparation and lithiation of 1-(3-bromopropyl)-2,6,7-trioxabicyclo[2.2.2]octane, see: Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.
(7) (a) Prepared from 2-carbomethoxy-4,4-dimethylcyclopentanone[7b-d] by selenylation (LiH, phenylselenylchloride) and oxidative elimination (*m*-CPBA). (b) Nikolaev, V. A.; Korobitsyna, I. K. *Zh. Org. Khim.* **1974**, *7*, 411. (c) Korobitsyna, I. K.; Nikolaev, V. A. *Zh. Org. Khim.* **1976**, *12*, 1245. (d) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728.
(8) All new compounds reported herein exhibited satisfactory spectral (IR, NMR), analytical, and/or high-resolution mass spectral characteristics. Supplementary material is available.
(9) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *46*, 4607. *N*-Phenyltrifluoromethanesulfonimide is available from PCR Chemicals, Gainesville, FL.
(10) (a) Binkley, E. S.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2156. (b) For preparation of triphenylmethallylstannane, see: Seyferth, D.; Weiner, M. *Ibid.* **1961**, *26*, 4797.
(11) For previous cuprate-mediated substitution reactions using vinyl triflates, see: McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313. For preparation of vinyl triflates, see: McMurry, J. E.; Scott, W. J. *Ibid.* **1983**, *24*, 979.
(12) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
(13) For a comprehensive discussion, see: Bailey, P. S. *Ozonation in Organic Chemistry*; Academic: New York, 1978; Vol. 1, pp 197-222.
(14) (a) Munavalli, S.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1964**, 729. (b) Bailey, P. S.; Hwang, H. H.; Chiang, C. Y. *J. Org. Chem.* **1985**, *50*, 231.
(15) (a) Carlsen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

Synthetic and Stereochemical Aspects of Intramolecular [4 + 2] Cycloadditions of *N*-Acyl Iminium Compounds with Alkene and Alkyne Dienophiles[†]

Summary: Boron trifluoride catalyzed intramolecular Diels-Alder cyclizations of *N*-acyl imines derived from simple aldehydes are stereospecific, affording trans-fused bicyclic 5,6-dihydro-1,3-oxazines.

Sir: Diels-Alder [4 + 2] cycloadditions of transient *N*-acyl imines, or the corresponding iminium complexes, with various alkenes to form 5,6-dihydro-1,3-oxazines are facile carbon-carbon bond-forming processes which have received surprisingly little attention from synthetic chemists (eq 1).[1] In the course of attempting to effect an intra-



(1)

molecular *N*-acyl imine ene reaction, we observed that glyoxylate-derived compound **1** cyclized thermally to afford dihydrooxazine lactone **2** in a totally stereospecific manner

[†]Dedicated to Professor George Büchi on the ocassion of his 65th birthday.

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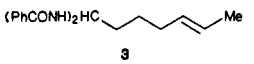
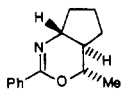
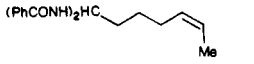
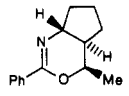
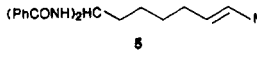
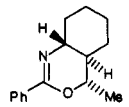
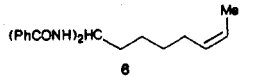
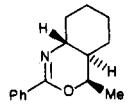
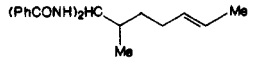
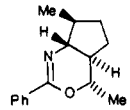
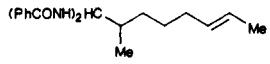
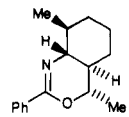
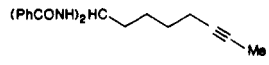
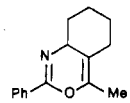
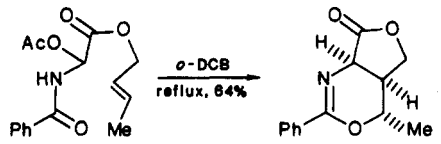
Table I

entry	bis-amide	product	yield, %[a]
1	 3	 10	87
2	 4	 11	78[b]
3	 5	 12	89
4	 6	 13	74
5	 7	 14	58
6	 8	 15	75
7	 9	 16	92

[a] Reactions were conducted in methylene chloride/room temperature, BF_3·Et_2O (2 equiv), 21–27 h. [b] Reaction run at 5 °C, BF_3·Et_2O (2 equiv), 71 h.

(eq 2).[2,3] This was the first reported example of an in-

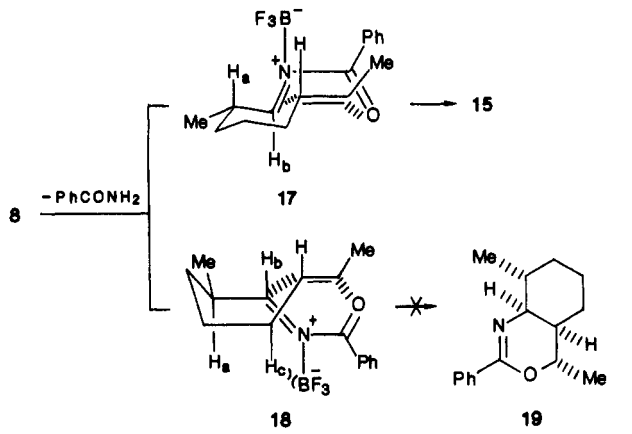


1 2 (2)

tramolecular [4 + 2] *N*-acyl imine cycloaddition.[4] Although this reaction produced a single stereoisomer, it is not clear if the cis ring fusion in adduct **2** results directly from the cycloaddition or is the product of a subsequent epimerization. Since we intend to eventually apply this methodology to natural product total synthesis, we have systematically explored various features of this Diels–Alder process which are described here.

One aspect which is particularly important to us with regard to future synthetic applications is whether *N*-acyl imines derived from simple *enolizable* aldehydes can be used successfully in these cycloadditions. Interestingly, only a single example of an intermolecular reaction of this

Scheme I



type exists.[5] In fact, such acyl imines are quite useful 4π cycloaddition components. Thus, we have prepared bis-amide alkenes **3–8** (Table I) by standard chemistry[6,7] from the corresponding aldehydes and have investigated cyclizations of these compounds.

Thermolysis of bis-amide **3** as in eq 2 resulted in elimination of benzamide and formation of an enamide which did not cyclize. However, treatment of **3** (or the enamide) with BF_3·Et_2O in CH_2Cl_2 afforded a good yield of *one* cycloaddition product which was proven by X-ray crystallography to have structure **10**, containing a trans ring fusion.[8] Similarly, *cis*-alkene **4** cyclized stereospecifically to provide trans-fused dihydrooxazine **11**.[9] Cycloadditions to afford six-membered carbocycles also proceeded cleanly, in all cases yielding trans-fused ring systems (**5** → **12**, **6** → **13**).[9]

It was also found that bis-amides **7** and **8**, which possess a chiral center in the connecting chain, cyclized stereospecifically to trans-fused products **14** and **15**,[9] respectively, having four contiguous chiral centers. Finally, alkyne **9** underwent cycloaddition to bicyclic oxazine **16** in high yield.[1,9]

We believe that these stereochemical results can best be rationalized by a consideration of nonbonded interactions in various Diels–Alder transition states[10] as exemplified for the conversion of **8** to **15** shown in Scheme I. Several assumptions have been made here. One is that the Lewis acid is complexed with the nitrogen lone pair of an intermediate *N*-acyl imine. Another is that the bridging chain methyl group is quasi-equatorial and that H_a and H_b are anti, as has been demonstrated in several related hetero[11] and all-carbon[12] intramolecular [4 + 2] cycloadditions. It would also appear that an (*E*)-*N*-acyl imine must be involved, since molecular models indicate tht the *Z* isomer cannot achieve the proper alignment for cyclization.[10]

Thus, we propose that cyclization of **8** proceeds via *N*-acyl iminium ion conformer **17** (Scheme I). The alternative transition state **18** which leads to cis isomer **19** is

(1) For excellent reviews, see: Schmidt, R. R. *Synthesis* **1972**, 333. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212.

(2) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.

(3) For some successful intramolecular *N*-acylimine ene reactions, see: Lin, J.-M.; Koch, K.; Fowler, F. W. *J. Org. Chem.* **1986**, *51*, 167. The systems reported in this paper are not properly disposed stereoelectronically for [4 + 2] cycloadditions to occur.

(4) For a possible exception, see: Eckhardt, H. H.; Perst, H. *Tetrahedron Lett.* **1979**, 2125.

(5) Giordano, C.; Abis, L. *Gazz. Chim. Ital.* **1974**, *104*, 1181.

(6) Giger, R.; Ben-Ishai, D. *Isr. J. Chem.* **1967**, *5*, 253.

(7) Breuer, S. W.; Bernath, T.; Ben-Ishai, D. *Tetrahedron* **1967**, *23*, 2869.

(8) We are grateful to Dr. M. Parvez for this determination.

(9) Established by ^1H NMR analysis.

(10) For mechanistic studies of this cycloaddition, see: Schmidt, R. R.; Machat, R. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 311. Schmidt, R. R.; Hoffmann, A. R. *Chem. Ber.* **1974**, *107*, 78.

(11) (a) Remiszewski, S. W.; Stouch, T. R.; Weinreb, S. M. *Tetrahedron* **1985**, *41*, 1173. (b) Remiszewski, S. W.; Whittle, R. R.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 3243. (c) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *Ibid.* **1983**, *48*, 3661.

(12) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992.

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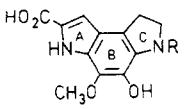
Diels-Alder Reactions of Heterocyclic Azadienes: Total Synthesis of PDE-II Methyl Ester

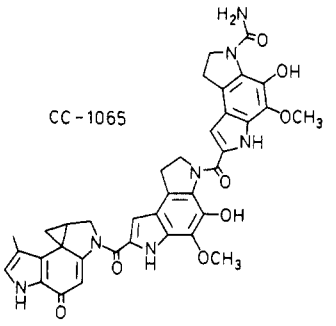
Summary: The total synthesis of the methyl ester of PDE-II (**2**), a 3',5'-c-AMP phosphodiesterase inhibitor constituting the central and right-hand 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole segment of the potent antitumor-antibiotic CC-1065, is described and is based on the utilization of two heterocyclic 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

(1) Enomoto, Y.; Furutani, Y.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *Agric. Biol. Chem.* **1978**, *42*, 1331.
(2) Nakamura, H.; Enomoto, Y.; Takeuchi, T.; Umezawa, H.; Iitaka, Y. *Agric. Biol. Chem.* **1978**, *42*, 1337.
(3) (a) Komoto, N.; Enomoto, Y.; Tanaka, Y.; Nitanai, K.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 559 (PDE-I). (b) Komoto, N.; Enomoto, Y.; Miyagaki, M.; Tanaka, Y.; Nitanai, K.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 555 (PDE-II).
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