bromine atom in **9** by cyano group was accomplished by the reaction with CuCN (*N*-methylpyrrolidone/150 °C/3 h; 47%)[13] to give the nitrile **10**. Catalytic osmylation ($OsO_4/Me_3N(O)/t$-BuOH/70 °C/1.5 h; 96%)[14] of **10** provided 5*R**,6*R**,1′*R** triol **11**,[15] mp 155 °C, as a single stereoisomer.[16]

Oxidative cyclization of the key intermediate **11** to the 2-oxabicyclo[2.2.2] compound **13**,[15] mp 163.5 °C, was achieved in 92% yield by the following improved procedure:[4] (i) trimethylsilation (excess MeCH=C(OMe)-$OSiMe_3/CH_2Cl_2$/reflux/20 min),[17] (ii) benzylic bromination (NBS/CCl_4/AIBN/sunlamp/60 °C/1 h; then HCl–THF to give **12**;[15] 96%), (iii) dehydrobromination ($AgClO_4$/THF/room temperature/20 min; 96%). The orientation of C(3)-Me in **13** as depicted (Scheme II) was supported by the ^1H NMR spectrum, which showed C-(3)-Me at δ 0.86 and C(3)-H at δ 3.77.[18] The nitrile **13** was then converted to the carboxamide **14**, mp 207 °C, in 90% yield by treatment with alkaline hydrogen peroxide.

The final stage of the synthesis, oxidation of **14** to the corresponding *p*-benzoquinone and subsequent introduction of amino group, turned out not to be straightforward. When **14** was converted to the cyclic 4,8-carbonate and treated with either ceric ammonium nitrate (CAN)[19] or AgO,[20] the substrate was recovered unchanged, in contrast to the case of a model compound, 1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-2-carboxamide, which did undergo facile oxidation to the corresponding benzoquinone. Consequently, **14** was subjected to demethylation (MeS-Li/DMF/155 °C/2 h; 70%),[21] and the resulting phenol **15** was reacted with CAN. Although **15** was readily oxidized to quinone, undefined overreactions associated with the free position ortho to the carboxamide group was difficult to suppress. However, after extensive investigations on the reaction course, we eventually succeeded in obtaining the target compound by carring out the controlled oxidation–in situ amination. Thus, **15** was first reacted with CAN (2 equiv) in MeCN at room temperature, and immediately after the disappearance of **15** (monitored by ^1H NMR or TLC), the reaction mixture was treated with NH_3/MeCN to give (±)-**1**, which was isolated by silica gel chromatography in 74% yield. The structure of the synthetic **1**, mp 214–215 °C, was confirmed by comparison of the spectral data (^1H NMR and mass) and the chromatographic behaviors (TLC and HPLC) with those of the natural product.

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Registry No. 1, 87392-60-7; 4, 75501-54-1; 5, 87338-25-8; 6, 87338-26-9; 7, 87338-27-0; 8, 87338-28-1; 9, 87338-29-2; 10, 87338-30-5; 11, 87338-31-6; 12, 87338-32-7; 13, 87338-33-8; 14, 87338-34-9; 15, 87338-35-0; 3-(2,5-dimethoxybenzoyl)propionic acid, 1084-74-8; vinyl bromide, 593-60-2.

Supplementary Material Available: Spectral and Analytical data for compounds **4–15** and **1** (4 pages). Ordering information is given on any current masthead page.

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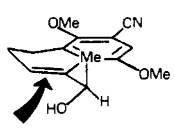
Received June 1, 1983

(13) Alternatively, **10** was prepared from **7** by the following sequence of reactions: (i) CuCN/*N*-methylpyrrolidone/150–160 °C/5 h; 97%), (ii) CH_2=CHMgBr (63%), (iii) $Hg(OAc)_2$-$NaBH_4$; Ac_2O-pyridine; aqueous NaOH (23%).

(14) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449–450.

(15) ^1H NMR spectral data (200 MHz, $CDCl_3$). **11**: δ 1.04 (3 H, d, *J* = 6 Hz, C-Me), 2.02 (2 H, m, H-7), 2.70 (1 H, br, OH), 2.75 (1 H, dt, *J* = 18, 7 Hz, H-8), 2.92 (1 H, dt, *J* = 18, 7 Hz, H-8), 3.27 (1 H, br, OH), 3.94 (3 H, s, OMe), 3.99 (3 H, s, OMe), 4.24 (1 H, t, *J* = 5 Hz, H-6), 4.50 (1 H, q, *J* = 6 Hz, H-1′), 4.90 (1 H, br, OH), 6.97 (1 H, s, ArH). **12**: δ 1.05 (3 H, d, *J* = 6 Hz, C-Me), 2.07 (1 H, ddd, *J* = 14, 12, 4 Hz, H-7), 2.42 (1 H, dt, *J* = 14, 4 Hz, H-7), 3.30 (3 H, br, OH), 3.90 (3 H, s, OMe), 4.22 (3 H, s, OMe), 4.91 (1 H, dd, *J* = 12, 4 Hz, H-8), 5.20 (1 H, q, *J* = 6 Hz, H-1′), 5.66 (1 H, t, *J* = 4 Hz, H-6), 7.06 (1 H, s, ArH). **13**: δ 0.86 (3 H, d, *J* = 6 Hz, C-Me), 1.46 (1 H, dt, *J* = 15, 2 Hz, H-7), 2.60 (1 H, d, *J* = 2 Hz, OH), 2.73 (1 H, ddd, *J* = 15, 8, 4 Hz, H-7), 3.77 (1 H, q, *J* = 6 Hz, H-3), 3.95 (3 H, s, OMe), 4.01 (4 H, overlapped OMe and H-8), 5.10 (1 H, dd, *J* = 4, 2 Hz, H-1), 5.73 (1 H, s, OH), 7.10 (1 H, s, ArH).

(16) Cf. the case of 1-(1-hydroxyethyl)-3,4-dihydronaphthalene, which gives a diastereomer ratio of (5*R**,6*R**,1′*R**)/(5*R**,6*R**,1′*S**) = ca. 2:1. The remarkable stereoselectivity observed with **10** could be rationalized by consideration of the preferred conformation A in which a steric interaction between the carbinol side chain and the 4-methoxy group would be minimized. Attack of OsO_4 from the less hindered α-face (arrow) to yield **11** would be highly favorable.



A

(17) Kita, Y.; Haruta, J.; Segawa, J.; Tamura, Y. *Tetrahedron Lett.* **1979**, 4311–4314.

(18) 3*S**-Isomer is expected to show C(3)-Me at δ ca. 1.4.

(19) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627–3629.

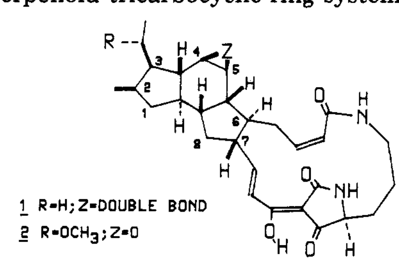
(20) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227–231.

(21) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859–3860.

Stereocontrol in the Intramolecular Diels–Alder Reaction. 5. Preparation of a Tetracyclic Intermediate for Ikarugamycin

Summary: The application of the intramolecular Diels–Alder strategy to the construction of a key tetracyclic intermediate **5** is described. Preparation of **5** allows for the control of all eight asymmetric centers present in the carbocyclic segment of ikarugamycin (**1**), an unusual macrocyclic tetramic acid antibiotic. The utility of transition-state selection influenced by preexisting asymmetric centers in the connecting chain was investigated.

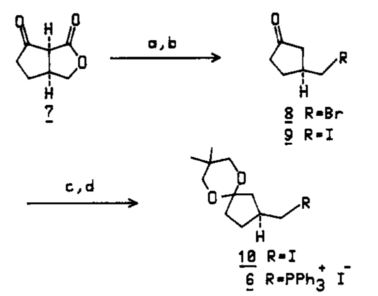
Sir: The structure and absolute configuration of (+)-ikarugamycin (**1**), an antiprotozoal antibiotic isolated by Jomon et al.[1] in 1972, was established on the basis of an elegant and carefully executed chemical structure proof by Ito and Hirata.[2] Ikarugamycin (**1**) and the related substance capsimycin (**2**) represent unusual structures, possessing a relatively rare macrocyclic lactam ring fused to a nonterpenoid tricarbocyclic ring system.[3]



(1) Jomon, K.; Kuroda, Y.; Ajisaika, M.; Saki, H. *J. Antibiot.* **1972**, *25*, 271.

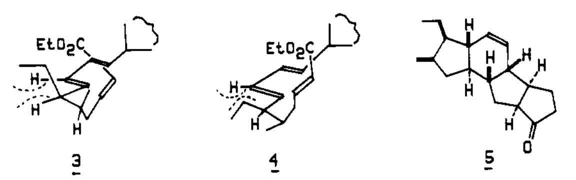
(2) (a) Ito, S.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1813. (b) Ito, S.; Hirata, Y. *Ibid.* **1977**, *50*, 227. (c) Ito, S.; Hirata, Y. *Tetrahedron Lett.* **1972**, *1181*. (d) Ito, S.; Hirata, Y. *Ibid.* **1972**, 1185. (e) Ito, S.; Hirata, Y. *Ibid.* **1972**, 2557.

Scheme I[a]



[a] Reagents: (a) $HBr/CH_2Cl_2/-78$ °C → room temperature/12 h then Δ/HOAc/1 h, (b) NaI/acetone/room temperature/40 h, (c) $HOH_2CC(CH_3)_2CH_2OH$/p-TsOH (catalyst)/PhH/Δ/9 h, (d) PPh_3(1.3 equiv)/$NaHCO_3$ (trace)/CH_3CN/Δ/96 h.

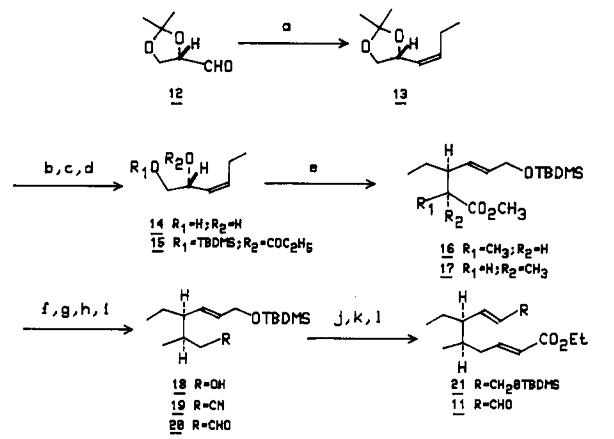
Furthermore, embedded within the macrocyclic lactam ring is a tetramic acid residue, which has been found to occur rarely in nature thus far.[4] The biosynthesis of 1 is suggested to proceed via the acetate pathway, with the further hypothesis that the carbocyclic residue arises via an intramolecular Diels–Alder reaction of a macrocyclic triene.[2,5] On the basis of this biogenetic hypothesis, we elected to construct the AB ring system via a less constrained intramolecular cycloaddition. Selection of endo transition state 3 rather than 4 (among four possible transition states) would afford the stereochemical relationship in the AB ring system found in 1. The two transition states 3 and 4 differ only with respect to the stereorelationship of the incoming dienophile with the side-chain groups. We anticipated that nonbonded interactions arising from these groups and other atoms in the diene unit would provide the necessary energetic differentiation of 3 and 4 and result in useful levels of stereoselection.[6,7]



Thus, we selected the tetracyclic cyclopentanone 5 as the initial target for our synthetic efforts. Ketone 5 encompasses all the required stereochemical features for conversion to 1 and possesses the masked precursors of the C-ring appendages in the form of the cyclopentanone ring.

Preparation of the two major subunits in the optically pure form is outlined in Schemes I and II. Phosphonium salt 6 was obtained, beginning with the antipode of the known bicyclic lactone 7[8] (α_D($CHCl_3$) +89.7°) by cleavage with HBr and decarboxylation to ketone 8 (83%). Conversion of 8 to 6 (amorphous solid, α_D(CH_3CN) −11.6°) then entailed halide exchange with NaI to the iodo ketone 9 (91%), ketalization with 2,2-dimethyl-1,3-propanediol to 10 (88%), and displacement with Ph_3P in hot acetonitrile (84%). Use of the more stable dimethylpropanediol ketal was required to avoid ketal cleavage during phosphonoum salt formation.

Scheme II[a]



[a] Reagents: (a) n-BuLi/n-$PrPPh_3^+Br^-$/THF/0 °C/1 h, (b) EtOH/1 N HCl/room temperature/12 h, (c) TBDMSCl/Et_3N/DMAP/CH_2Cl_2/0 °C → room temperature/7 h, (d) propionyl chloride/pyridine/CH_2Cl_2/0 °C → room temperature/15 h, (e) LDA/23% HMPA-THF/−78 °C; Me_3SiCl/−78 °C → room temperature/20 h; H_3O^+; CH_2N_2, (f) Dibal-H/THF/0 °C/1 h, (g) TsCl/pyridine/CH_2Cl_2/0 °C → room temperature/40 h, (h) KCN/Me_2SO/80 °C/5 h, (i) Dibal-H/Et_2O/−20 °C/0.5 h; 5% HOAc-NaOAc (aqueous buffer)-THF-MeOH (1:1:1)/room temperature/3 h, (j) NaH/$(EtO)_2P(O)CH_2CO_2Et$/−50 → 0 °C/2 h, (k) THF-H_2O-HOAc (1:1:1)/room temperature/16 h, (l) PDC/CH_2Cl_2/room temperature/12 h.

The aldehyde fragment 11 was obtained from (S)-(−)-glyceraldehyde acetonide (12).[10] Initially, condensation with ethylidenetriphenylphosphorane at 0 °C provided, with a high degree of stereoselectivity, the olefinic acetonide 13 in 67% yield.[11] After acidic hydrolysis to diol 14 (83%), successive silylation with t-Bu$(CH_3)_2$SiCl in the

(3) Seto, H.; Yonehara, H.; Aizawa, S.; Clardy, J.; Arnold, E.; Tanabe, M.; Urano, S. *Koen Yoshishu-Tennen Yuki Kagobutsu Toronkai 22nd* **1979**, 394; *Chem. Abstr.* **1981**, *92*, 211459u.

(4) Van Der Bann, J. L.; Barhick, J. W. F. K.; Bickelhaupt, F. *Tetrahedron* **1978**, *34*, 223.

(5) The early stages of the biogenetic hypothesis have been verified (cf. ref 3).

(6) The use of the intramolecular Diels–Alder strategy has been reviewed by the following: (a) Carlson, R. *Ann. Rep. Med. Chem.* **1973**, *9*, 270. (b) Oppolzer, W. *Angew Chem., Int. Ed. Engl.* **1977**, *16*, 10. (c) Breiger, G.; Bennet, J. N. *Chem. Rev.* **1980**, *80*, 63.

(7) Recently in work directed toward X-14547A, similar cyclizations have been performed and the major products were shown to possess the expected cis relationship between the ethyl group and ring junction proton: (a) Edwards, M. P.; Ley, S. V.; Lister, S. G. *Tetrahedron Lett.* **1981**, *21*, 361. (b) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 6969. (c) Roush, W. R.; Meyers, A. G. *J. Org. Chem.* **1981**, *46*, 1509. (d) Boeckman, R. K., Jr.; Demko, D. M., unpublished results.

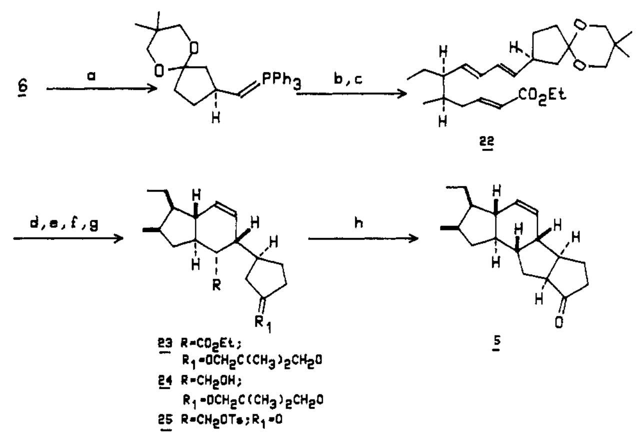
(8) Lactone 7 was prepared via the route that we have described previously, employing the antipode of the chiral auxiliary used previously (cf. ref. 8b). The required optical isomer of the acrylic ester of (1S,2R,5S)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexanol was obtained by esterification of the alcohol (acryloyl chloride/Et_3N/DMAP) that was obtained from (+)-pulegone by a modification of the published procedure (cf. ref 8a): (a) Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Org. Chem.* **1978**, *43*, 1610. (b) Boeckman, R. K.; Naegely, P. C.; Arthur, S. D. *Ibid.* **1980**, *45*, 752.

(9) Partial spectral data: (**5**) ^{1}H NMR (400 MHz) δ 0.68 (1 H, d. of t, J = 6.5, 13 Hz), 0.89 (3 H, d, J = 7 Hz), 0.93 (3 H, t, J = 7 Hz), 5.76 (1 H, d of t, J = 10, 2 Hz), 5.88 (1 H, d, J = 10 Hz); (**11**) ^{1}H NMR (90 MHz) δ 0.86 (6 H, overlapping d and t, J = 7 Hz), 1.27 (3 H, t, J = 8 Hz), 4.13 (2 H, q, J = 8 Hz), 5.80 (1 H, d, J = 16.5 Hz), 6.03 (1 H, d of d, J = 15, 7.5 Hz), 6.59 (1 H, d of d, J = 16.5, 9 Hz), 6.83 (1 H overlapping d of t, J = 16.5, 7.5 Hz), 9.50 (1 H, d, J = 9 Hz); (**6**) ^{1}H NMR (90 MHz) δ 0.88 (6 H, s), 1.45–2.50 (7 H, m), 3.30 (2 H, s), 3.39 (2 H, s), 3.76 (2 H, d of d, J = 15, 6 Hz), 7.50–8.00 (15 H, m); (**22**) ^{1}H NMR (400 MHz) δ 0.78–0.86 (6 H, m), 0.94 (3 H, s), 0.99 (3 H, s), 1.28 (3 H, t, J = 8 Hz), 1.30–3.60 (13 H, m), 3.46 (2 H, s), 3.48 (2 H, s), 4.19 (2 H, q, J = 8 Hz), 5.33 (1 H, d of d, J = 10, 16 Hz), 5.54 (1 H, d of d, J = 8, 16 Hz), 5.81 (1 H, d, J = 16.5 Hz), 5.88–6.04 (2 H, m), 6.92 (1 H, overlapping d of t, J = 16.5, 7.5 Hz); (**23**) ^{1}H NMR (90 MHz) δ 0.67–1.10 (12 H, m), 1.23 (3 H, t, J = 8 Hz), 1.24–2.80 (17 H, m), 3.40 (4 H, br s), 4.10 (2 H, q, J = 8 Hz), 5.57, 5.87 (2 H, AB q, J = 9 Hz).

(10) Prepared from ascorbic acid (vitamin C) by a modification of the method of Jung and Shaw: Jung, M. E.; Shaw, T. J. *J. Am. Chem Soc.* **1980**, *102*, 6304.

(11) The ratio of Z to E olefin was >98:2 under these conditions.

Scheme III[a]



[a] Reagents: (a) n-BuLi/THF-HMPA (10:1)/-50 °C $\rightarrow$ room temperature/1 h, (b) 11/$-50 \rightarrow 0$ °C/2 h, (c) I_2 (0.2 equiv)/hexane/room temperature/6 h, (d) BHT/$PhCH_3$/140 °C/70 h, (e) Dibal-H/THF/0 °C/1.5 h, (f) 0.5 N HCl-THF (1:1)/room temperature/16 h, (g) TsCl/pyridine/CH_2Cl_2/4 °C/40 h, (h) t-BuOK/t-BuOH-PhH (1:2)/room temperature/20 h.

presence of 4-(dimethylamino)pyridine[12] and acylation with propionyl chloride in pyridine/CH_2Cl_2 afforded allylic ester **15** (63% overall yield).

The crucial erythro relationship of the C-2, C-3 alkyl groups was then established via use of the ester enolate Claisen rearrangement.[13] Thus, treatment of **15** with LDA/23% HMPA-THF at -78 °C followed by trapping with Me_3SiCl and warming to room temperature provided, after esterification (CH_2N_2), the esters **16** and **17** (86:14) in 74% yield.[14]

Dibal-H reduction of **16** in THF smoothly afforded alcohol **18** (92%), which was homologated to nitrile **19** by using standard methods (61% overall yield from **18**). Reduction of nitrile **19** with Dibal-H (1.4 equiv) in ether followed by hydrolysis (HOAc/NaOAc in CH_3OH-THF-H_2O (1:1:1)[15] produced the aldehyde **10** which was immediately subjected to condensation with sodium ethyl (diethylphosphinyl)acetate to provide exclusively the E ester **21** in 77% overall yield. Finally, conversion to ester aldehyde **11** (oil, $\alpha_D(CHCl_3)$ $-26.4°$) was effected in 84% overall yield by hydrolysis of **20** in aqueous acetic acid and oxidation of the resulting allylic alcohol with pyridinium dichromate (PDC) in CH_2Cl_2.[9]

Final assembly of the E,E triene ester **22** required for the key cycloaddition was accomplished (Scheme III) by condensation of the ylide, derived from **6** by treatment with n-BuLi (-50 °C $\rightarrow$ room temperatuare) in THF-HMPA (10:1), with **11** at $-50 \rightarrow 0$ °C over 2 h, and isomerization of the initially formed mixture of dienes (E,Z/E,E, 2:1) to the pure E,E diene **22** by exposure to I_2 (catalytic amount) in hexane for 6 h (87% overall yield from **11**).[16]

Triene ester **22** underwent smooth cyclization at 140 °C (70 h), providing bicyclic ester **23** as the major stereoisomer (>5:1) in 87% total yield.[9,17] Reduction of **23** with Dibal-H in THF gave the crystalline alcohol **24** (mp 127–128 °C) in 87% yield. Closure of the final bond was affected by acidic hydrolysis of ketal **24** (82%), conversion to the crystalline tosylate **25** (mp 147–148 °C) in 72% yield in the usual manner, and cyclization with t-BuOK in PhH-t-BuOH, which afforded the desired tetracyclic ketone **5** (mp 65–67 °C; $\alpha_D(CHCl_3)$ +103°) in 92% yield.[18]

The stereochemistry of **5** was established to be that depicted by a combination of difference decoupling and difference NOE measurements at 400 MHz. These experiments revealed the position of the axial angular proton adjacent to the ethyl group, which had the expected large (12 Hz) coupling with the trans ring junction proton. Furthermore, upon irradiation of the secondary methyl group, this same proton (as well as the methylene protons of the ethyl group) showed the expected NOE enhancement. These data uniquely define the cis relationship of the ethyl group, methyl group, and ring junction proton as well as the trans ring junction stereochemistry. The data rules out the products from the alternative exo and endo transition states, which would be expected to lack the NOE effect and/or have a small ring junction coupling constant (cis).

Studies are now underway toward the optimization of the above synthetic route to **5**. Conversion of **5** with its eight contiguous asymmetric centers to ikarugamycin via initial oxidative cleavage of **5** and epimerization to a more stable trans relationship of the substituents at C-6 and C-7[19] is also under investigation.

Acknowledgment. This investigation was supported by grants (CHE-80-05176 and CHE-81-19823) from the National Science Foundation and a PHS Fellowship to J. J. Napier (CA-06850), from the National Cancer Institute, CHHS, for which we are very grateful.

(12) Chavdhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

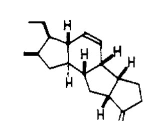
(13) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(14) The diastereomeric ratio of **16**/**17** was determined by integration of the ^1H NMR (400 MHz) spectrum; the mixture was not separable and was used as such in succeeding steps. Alternatively, **17** was the major product when enolization was performed in THF solution.

(15) Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945.

(16) Alder, K.; Vogt, W. *Justus Liebigs Ann. Chem.* **1951**, *571*, 137.

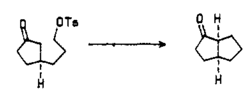
(17) Determined by examination of olefin region of ^1H NMR (400 MHz) spectra of compounds **23** and **5**. Note, if optically active **11** is reacted with racemic **6** a 1:1 mixture of **5** and **i** is eventually obtained.



i

This result implies that the adjacent asymmetric center of the cyclopentyl group exerts no influence on the stereochemical outcome of the Diels–Alder cyclization.

(18) The alkylation was expected to provide the fused ring product on the basis of cyclization of model compound **ii** to bicyclic ketone **iii** in high



ii iii

yield. This result was corroborated by a correlation of ^{13}C carbonyl chemical shifts in **5**, **i**, and **iii**.

(19) For an example of a similar epimerization in a prostaglandin synthesis, see Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265.

(20) Fellow of the A. P. Sloan Foundation, 1976–1980. Recipient of a Research Career Development Award (CA-00273, CA-00702) from the National Cancer Institute for the National Institutes of Health.

(21) These studies were conducted in part in the Chemistry Department of Wayne State University, Detroit, MI.

(22) NIH postdoctoral fellow, 1981–1983.

(23) E.W.T. acknowledges the receipt of a University Fellowship for 1974–1976 from Wayne State University.

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