For the route to L-acosamine, the amino group should be disposed in an opposite configuration of that of **7b**. This was realized by opening of the epoxide ring of (−)-**6** with tosylate to give **8a** (R = H) (78% yield, [mp 51–52 °C, $[\alpha]_D^{10}$ +7.4° (*c* 0.6, $CHCl_3$)]. Ketal protection of the diol **8a** with cyclohexanone followed by displacement with NaN_3 afforded in 74% yield the ketal protected azidodiol **15**, which was further treated with LAH and followed by acid hydrolysis and benzoylation to yield **9** [65% yield, $[\alpha]_D^{20}$ −13.8° (*c* 0.5, EtOH), (lit.[11] $[\alpha]_D^{20}$ −14.5° (*c* 1, EtOH))], a known precursor of acosamine.[11] The tosylate opening of the epoxyalcohol (−)-**6** proceeded very slowly with the conventional LPTS-Ti(O-*i*-Pr)$_4$. This reaction can only be effected by LPTS-PTS reagent.[18] The tosylate opening here again occurs exclusively at C_3.

The routes to daunosamine and epidaunosamine comprise entirely the same reactions with an only exception of an added Mitsunobu transformation of the C_1 configuration[14] (procedures i and j of Scheme I). The epoxybenzoate **10a** (R = PhCO) [$[\alpha]_D^{10}$ +35.4° (*c* 0.5, $CHCl_3$)] was obtained in 86% yield, which was transformed to **11** [47% yield, mp 134–135 °C, $[\alpha]_D^{10}$ +20.5° (*c* 0.5, EtOH) (lit.[11] $[\alpha]_D^{20}$ +21° (*c* 1, EtOH))]. An intramolecular migration of a benzoyl group from O to N was involved in this step. The epoxyalcohol **10b** [$[\alpha]_D^{20}$ +40.5° (*c* 0.5, CH_2Cl_2)] was obtained in 73% yield and underwent oxirane opening by tosylate to a monotosylate **12a** (R = H) [82% yield, mp 83–85 °C, $[\alpha]_D^{20}$ +12.1° (*c* 0.5, $CHCl_3$)]. In four steps and 49% overall yield, **12a** was transformed to **13** $[\alpha]_D^{10}$ +30° (*c* 0.5, EtOH)]. Compound **11** can be transformed to daunosamine (**1**) by a known ozonolysis procedure.[11] **13**[15] was subjected to ozonolysis and afforded an *N*-benzoyl-**4** [77% yield, mp 216–217 °C, $[\alpha]_D^{10}$ −55.0° (*c* 0.1, EtOH) (lit.[16] $[\alpha]_D^{20}$ −58.5° (*c* 0.25, EtOH) mp 215–218 °C)].

The D-isomers of the whole family can also be obtained either by exchanging L-(+)-DIPT in procedure a with D-(−)-DIPT in procedure h or by adding a Mitsunobu transformation in the right-hand side of Scheme I (that is transform (−)-**6** to (+)-**11**) and omit the Mitsunobu reaction in the left-hand side of Scheme I. Indeed, the antipode of **11** was obtained in 52% yield from (−)-**10a**, with an opposite rotation value of that of **11**, $[\alpha]_D^{10}$ −19.5 (*c* 0.5, EtOH).

In addition, the *N*-methyl or *N*,*N*-dimethyl isomers (namely, rhodasamine, R^1 = *N*,*N*-dimethyl in L-**1**, actinosamine, R^1 = *N*-methyl in L-**2**, megosamine, R^2 = *N*,*N*-dimethyl in L-**3**, angolosamine, R^1 = *N*,*N*-dimethyl in D-**2**) can be produced by opening of the epoxide ring with methyl or dimethylamine instead of opening by methanolic ammonia. One of them, a precursor of megosamine was prepared by treating (−)-**6** with dimethylamine in a sealed tube and after benzoylation, yielded a monobenzoyl–dimethylamino analogue of **7a** in 52% yield, $[\alpha]_D^{10}$ +18.3° (*c* 1.5, EtOH).[17]

Acknowledgment. This project is supported by The National Natural Science Foundation of China and Chinese Academy of Sciences.

(12) Owing to the discrepancy of the specific optical rotations, **7b** was subjected to ozonolysis and gave the benzoylristosamine on further treatment in 75% yield [$[\alpha]_D^{10}$ −15.3° (*c* 0.5, EtOH) 5 min, (lit.[11] $[\alpha]_D^{20}$ −12.5° (*c* 1, EtOH) 10 min)]. The ^{13}C NMR of benzoylristosamine obtained here showed the same spectra with known data. On correlating the value of the specific optical rotations of **7b**, **9**, **11**, and **13**, we are further convinced that the [α] value of −3.9 of **7b** is correct.

(13) (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Dai, L. X.; Lou, B. L.; Zhang, Y. Z.; Guo, G. Z. *Tetrahedron Lett.* **1986**, *27*, 4343.

(14) Mitsunobu, O. *Synthesis* **1981**, 1.

(15) **13** has been obtained[11] as a minor component and has been transformed to a mixture of *N*-benzoyl derivatives of **1** and **4**. No data of **13** has been given.

(16) Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, *20*, 3883.

(17) Satisfactory spectroscopic data and elemental compositions were obtained for all new compounds.

(18) LPTS = 2,6-lutidinium *p*-toluenesulfonate; DEAD = diethyl azodicarboxylate.

Stereocontrolled Total Synthesis of (±)-Quinocarcin

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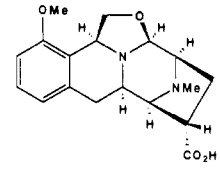
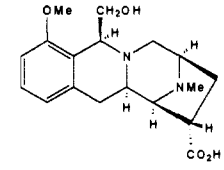
Received February 29, 1988

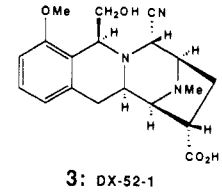
Since its initial isolation by Takahashi and Tomita[1] in 1983, the antitumor antibiotic quinocarcin (**1**) and its inactive congener quinocarcinol (**2**), have attracted considerable synthetic attention.[2]



1: Quinocarcin



2: Quinocarcinol



3: DX-52-1

Although little is known of the mechanism of action of quinocarcin, it seems likely that the compound may act as a site specific catalyst for superoxide generation, much like the quinone antibiotics. As a result, it exhibits strong activity against P388 lymphocytic leukemia in mice while displaying a rather restricted antibacterial spectrum.[3] Although the synthesis of quinocarcinol was achieved in 1985,[2a] the instability inherent in the oxazolidine of the title compound proved a demanding obstacle to the successful synthesis of quinocarcin. Herein we report the first total synthesis of the novel molecule via the key intermediate DX-52-1 (**3**), a cyano derivative first synthesized from the natural product by investigators at Kyowa Hakko in Japan.[2b] DX-52-1 afforded an excellent subtarget, possessing the requisite stability for appropriate skeletal manipulations while providing easy access to the aforementioned oxazolidine of this complex structure.

Condensation of the readily available aldehyde **4**[4] and piperazinedione **5**[5] (*t*-BuOK/*t*-BuOH, THF, −78 °C),[6] followed by ammonolysis (NH_3, MeOH), provided the unsymmetrical piperazinedione **6** in 81% yield (Scheme I). Selective activation of the amide nitrogen (CbzCl, DMAP, Et_3N, CH_2Cl_2, −20 °C, 24 h, 82%) to give **7** allowed for the construction of a diazabicyclo[3.2.1] system utilizing a three-step protocol. First, partial amide carbonyl reduction ($NaBH_4$, MeOH/CH_2Cl_2, −20 °C), followed by acyliminium ion-mediated cyclization ($HgCl_2$, CSA, CH_3CN/H_2O, 40 °C, 20 min), and finally reduction of the resultant aldehyde ($NaBH_4$, MeOH/CH_2Cl_2, 0 °C) gave the alcohol **8** in 59% yield. With the bicyclic system in place, reduction of the exocyclic double bond (Ra–Ni (W2), H_2 (2000 psi), EtOH, 100 °C, 1.5 h) could be effected from the less hindered α-face of the molecule. Immediate in situ reprotection of the amine[7]

(1) (a) Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, *36*, 468. (b) Tomita, F.; Takahashi, F.; Shimizu, K. *J. Antibiot.* **1983**, *36*, 463.

(2) (a) Danishefsky, S. J.; Harrison, P. J.; Webb, R. R.; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1423. (b) Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065. (c) Williams, R. M.; Ehrlich, P. P.; Zhai, W.; Hendrix, J. *J. Org. Chem.* **1987**, *52*, 2615. (d) Kiss, M.; Russel-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187.

(3) Tomita, F.; Takahashi, K.; Tamaoki, T. *J. Antibiot.* **1984**, *37*, 1268.

(4) Prepared from commercially available *m*-hydroxybenzaldehyde (dimethylthexylsilyl chloride (DMTSCl), *i*-Pr_2NEt, $ClCH_2CH_2Cl$, 70 °C).

(5) Prepared in seven steps from commercially available diethylacetamidomalonate in 39% overall yield: (1) propargyl bromide, NaH, DMF; (2) 3 N HCl, reflux; (3) MeOH, 12 N HCl, reflux; (4) $ClCH_2COCl$, $NaHCO_3$, Et_2O/H_2O; (5) NH_3, MeOH, 140 °C; (6) Ac_2O, reflux; (7) PhSH, AIBN, benzene.

(6) A modification of the original procedure which provided improved yields. See: Gallina, C.; Liberatori, A. *Tetrahedron* **1974**, *30*, 667.

(7) For subsequent opening of the bicyclic lactam it was crucial that some electron-withdrawing group be affixed to this amine nitrogen.

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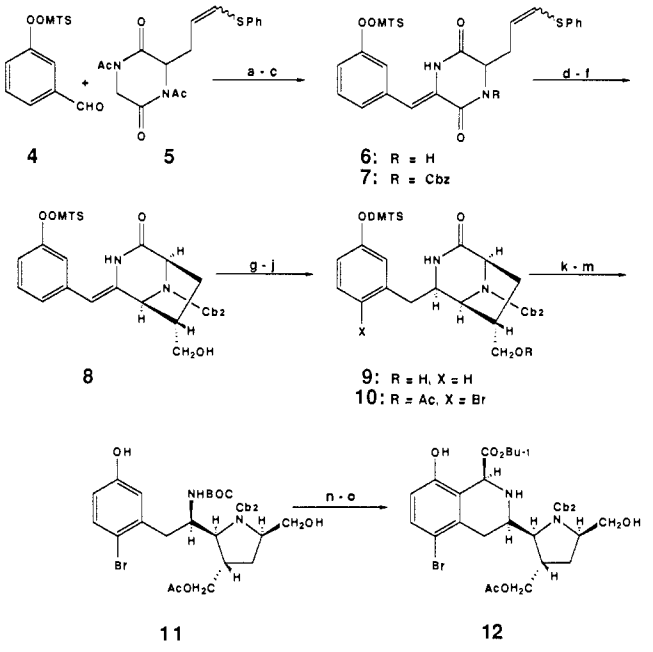
Scheme I[a]

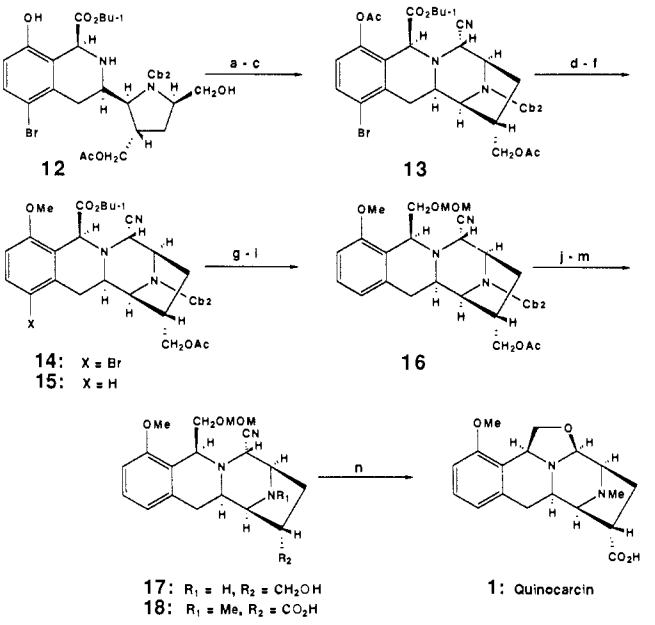


[a] (a) 1 M *t*-BuOK/*t*-BuOH, THF, −78 °C. (b) NH_3, MeOH, room temperature. (c) CbzCl (1.5 equiv), DMAP (0.5 equiv.), Et_3N (20) equiv), CH_2Cl_2, −20 °C. (d) $NaBH_4$, MeOH/CH_2Cl_2 (1:1), −20 °C. (e) $HgCl_2$, CSA, CH_3CN/H_2O (9:1), 40 °C. (f) $NaBH_4$, MeOH/CH_2Cl_2 (1:1), 0 °C. (g) Ra–Ni (W2), H_2 (2000 psi), EtOH, 100 °C. (h) CbzCl (1.1 equiv) $NaHCO_3$ (1.5 equiv), EtOH, room temperature. (i) Br_2, CH_2Cl_2, room temperature. (j) Ac_2O/Py (1:1), 60 °C. (k) (*t*-BuOCO)$_2$O (2 equiv), DMAP (0.5 equiv), Et_3N (5 equiv), $ClCH_2CH_2Cl$, 80 °C. (l) $NaBH_4$, MeOH, 0 °C. (m) *n*-Bu_4NF, THF, room temperature. (n) TFA, room temperature. (o) *t*-BuOCOCHO (10 equiv), MeOH, 120 °C.

(CbzCl, $NaHCO_3$, EtOH) thus provided the saturated bicyclic lactam **9** as a single compound in 74% yield. So as to prevent any formation of unwanted tetrahydroisoquinoline isomer, the intermediate was next brominated[8] (Br_2, CH_2Cl_2, room temperature, 78%) and immediately acetylated (Ac_2O/Py, 60 °C, 10 min, 100%) to provide compound **10** as a single regioisomer. Next, the amide was converted to the pyrrolidine **11** in preparation for construction of the tetrahydroisoquinoline. This was accomplished by first activating the lactam ((*t*-BuOCO)$_2$O, DMAP, Et_3N, $ClCH_2CH_2Cl$, 80 °C, 30 min, 92%),[9] then opening the bicyclic system ($NaBH_4$, MeOH, 0 °C, 97%),[10] and finally removing the phenolic silyl ether (*n*-Bu_4NF, THF, room temperature, 97%).[11] After deprotecting the BOC group (TFA, room temperature), the critical Pictet–Spengler cyclization was achieved by subjecting the amine salt to 10 equiv of *tert*-butyl glyoxylate in MeOH for 20 min at 120 °C. These conditions provided an 8:1 mixture of predominantly desired isomer **12** in 86% yield.[12]

Selective protection of phenol **12** (Ac_2O, K_2CO_3, acetone, room temperature, 2 h, 83%) allowed for Swern oxidation[13] of the alcohol and formation of the tetracyclic nitrile **13** (Me_3SiCN, $ZnCl_2$, CH_2Cl_2, room temperature) in 74% yield (Scheme II). Interestingly, attempts to directly methylate phenol **12**, whereas they did bring about formation of the methyl ether with little N-methylation, led to extensive epimerization of the *tert*-butyl

Scheme II[a]



[a] (a) Ac_2O, K_2CO_3 (5 equiv), acetone, room temperature. (b) (COCl)$_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N. (c) Me_3SiCN, $ZnCl_2$, CH_2Cl_2, room temperature. (d) $NaHCO_3$ (5 equiv), MeOH, room temperature. (e) MeI (1.5 equiv), K_2CO_3 (5 equiv), acetone, 60 °C. (f) *n*-Bu_3SnH (1.2 equiv), AIBN (0.3 equiv), $PhCH_3$, 120 °C. (g) TFA, room temperature. (h) *i*-BuOCOCl (10 equiv), Et_3N (3 equiv), CH_2Cl_2, 0 °C; $NaBH_4$, MeOH, 0 °C. (i) $MeOCH_2Cl$ (3 equiv), Et_3N (5 equiv), CH_2Cl_2, 80 °C. (j) 3 N NaOH, MeOH, room temperature. (k) 10% Pd–C, H_2 (1 atm), EtOH, room temperature. (l) MeI (2 equiv), *i*-Pr_2NEt (5 equiv), CH_3CN, 60 °C. (m) Jones reagent, acetone, room temperature. (n) Me_3SiCl, NaI, CH_3CN; $AgNO_3$, MeOH/H_2O (4:1), room temperature.

ester.[14] Selective phenolic acetate deprotection ($NaHCO_3$, MeOH, room temperature, 2 h) and subsequent methyl ether formation (MeI, K_2CO_3, acetone, 60 °C, 2.5 h) gave intermediate **14** in 89% yield.[15] Debromination was conveniently accomplished by using radical reduction conditions (*n*-Bu_3SnH, AIBN, $PhCH_3$, 120 °C, 15 min, 92%) to provide compound **15**.[16] A three-step sequence accomplished the reduction of the *tert*-butyl ester and protection of the resultant hydroxymethyl group. First, the *tert*-butyl ester was deprotected (TFA, room temperature). Then, via the mixed anhydride, the intermediate carboxylic acid was reduced (*i*-BuOCOCl, Et_3N, CH_2Cl_2, 0 °C, then $NaBH_4$, MeOH, 0 °C, 81%). Finally, the alcohol was protected ($MeOCH_2Cl$, Et_3N, CH_2Cl_2, 80 °C, 90%) to provide compound **16**. Acetate hydrolysis (3 N NaOH, MeOH, room temperature) precluded acyl transfer in the subsequent hydrogenolysis (10% Pd–C, H_2 (1 atm), EtOH, 30 min, 78%) and provided compound **17**. This compound was in turn methylated[17] (MeI, *i*-Pr_2NEt, CH_3CN, 60 °C, 3 h, 93%) and subsequently oxidized to furnish MOM protected DX-52-1, compound **18**, in 77% yield. Final conversion of this intermediate to quinocarcin was achieved in a two-step process. Utilizing Me_3SiI (Me_3SiCl, NaI, CH_3CN, room temperature), this intermediate was first converted to the critical DX-52-1 subtarget, which, upon exposure to a solution of $AgNO_3$ in MeOH/H_2O, furnished the title compound in 70% yield. Synthetic quinocarcin (**1**) was identical with an authentic sample

(8) For example, see: Kametani, T.; Kobari, T.; Fukumoto, K.; Fujihara, M. *J. Chem. Soc. C* **1971**, 1796.

(9) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2425.

(10) Attempts at partial reduction of the lactam and subsequent trapping of the aldehyde met with little success.

(11) The silyl ether proved to be unusually stable. Heating with TFA at 60 °C for prolonged periods in an attempt at a dual deprotection gave no deprotected phenol.

(12) Attempts to carry out this cyclization with unactivated aldehydes, e.g., $BnOCH_2CHO$, gave poor results and little stereocontrol.

(13) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(14) The mild conditions of the acetylation reaction produced no such epimerization. Since epimerization could not easily be achieved after protection of the phenol, it seems likely that a retro-Michael–Michael type process rather than a deprotonation–protonation process is involved here.

(15) These conditions, similar to those which gave extensive epimerization on phenol **12**, gave no such results with the tetracyclic phenol.

(16) Removal of bromine under hydrogenolytic conditions led to extensive nitrile reduction.

(17) Attempts to introduce the methyl group under conventional reductive conditions (i.e., with formaldehyde) were complicated by formation of an unusually stable oxazine.

in both TLC behavior and spectroscopic properties.[18,19]

Acknowledgment. This work was supported by the National Institutes of Health (Grant CA28119). We thank Drs. T. Hirata, M. Kasai, and H. Saito of Kyowa Hakko for valuable information.

Supplementary Material Available: Experimental details and copies of NMR spectra of key intermediates and synthetic quinocarcin (24 pages). Ordering information is given on any current masthead page.

(18) We were aware of the possibility of dramatic changes in the NMR of the final compound depending on the pH of the solution. In fact we found it necessary to separate a sample of authentic quinocarcin utilizing the exact procedure used in separation of the synthetic sample in order to obtain identical NMR spectra.

(19) We are indebted to Dr. T. Hirata of Kyowa Hakko Kogyo Co., Ltd., Tokyo, for samples of authentic quinocarcin and DX-52-1.

Synthetic Studies in the Brefeldin Series: Asymmetric Enamine–Enal Cycloaddition and Intramolecular Nozaki Reactions

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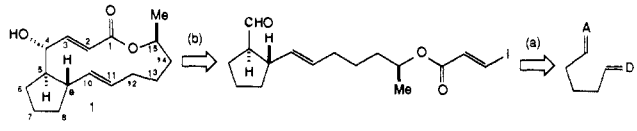
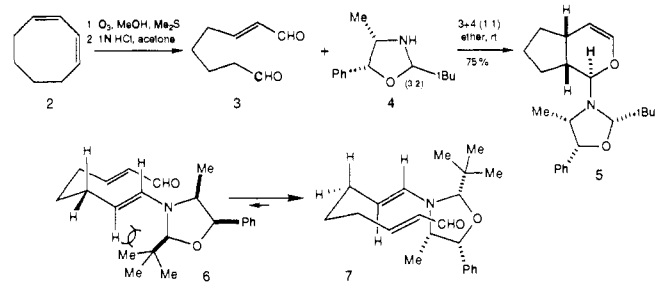
Received December 29, 1987

We recently reported on our stereochemical studies of the intramolecular enamine–enal cycloaddition reaction.[1] In continuation of these efforts, we have been engaged in studies directed toward the asymmetric synthesis of brefeldin C[2] and stereoisomers. We now describe (a) the utilization of a chiral amine in the cycloaddition reaction as a means to acquire carbocyclic ring systems in nonracemic form and (b) the diastereoselective *macroannelation* of enantiomeric five-membered carbocycles via a chromium-mediated coupling reaction.[3] The combination of these reaction processes has resulted in the first enantioselective synthesis of the macrolide antibiotic (+)-brefeldin C.

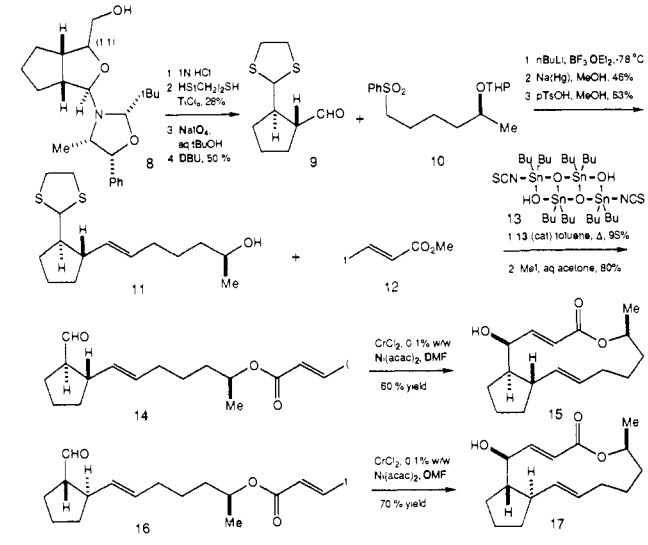


The cyclization substrate **3** was readily prepared from 1,3-cyclooctadiene by controlled ozonolysis. Earlier, we had shown that **3** undergoes a [4 + 2] cycloaddition of an in situ generated enamine with the enal function when treated with an achiral secondary amine (e.g., *N*-methylaniline).[1] We have now screened chiral secondary amines for their ability to promote cycloaddition with high levels of stereoinduction. Optimal results were obtained with oxazolidines derived from the condensation of pivalaldehyde with (+)- or (−)-norephedrin.[4] The reaction of a 1:1 mixture

Scheme I



Scheme II



of **3** and **4** (as a 3:2 ratio of isomers) proceeded to completion over a 12-h period at room temperature to provide a 17:1 ratio of two cycloadducts **5** (Scheme I). The cis stereochemistry of the oxazolidine ring substituents of the major isomer ($[\alpha]^{27}_D = -120.2$, ether) was determined by NOEDS experiments and is consistent with the stereochemistry of oxazolidines derived from the condensation of ephedrine and aldehydes.[5] The relative stereochemistry of the bicyclic dihydropyran is in accord with our earlier studies; the absolute stereochemistry was tentatively assigned as depicted based on an evaluation of the enamine intermediate (Si face selectivity at β-carbon of enamine **7** leads to product; rotamer **6** suffers steric interference with the *tert*-butyl substituent)[6] and later confirmed by the conversion of **5** into (+)-brefeldin C. The stage at which enrichment of cis stereochemistry (about the oxazolidine ring) occurs is not known.

The cycloaddition reaction is well suited for the asymmetric synthesis of vicinally substituted cyclopentyl ring systems. The synthesis of trans disubstituted precursors to brefeldin C isomers is shown in Scheme II. The oxidation of **5** with mCPBA in methanol buffered with pyridine was followed by an in situ reduction with $NaBH_4$ to afford **8** in 31% overall yield. Hydrolysis, thioacetalization, and diol cleavage provided a monothioacetal of *cis*-(meso)-dialdehyde in >90% ee. For the present application the trans isomer was required; accordingly, the cis isomer was epimerized with DBU to afford **9** ($[\alpha]^{27}_D = -40.7$, ether; trans/cis > 25:1). A Julia olefination[7] was achieved by the action of

(1) Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274.

(2) Isolation and structure elucidation: (a) Sunagawa, M.; Ohta, T.; Nozoe, S. *Heterocycles* **1979**, *13*, 267. Biosynthetic studies: (b) Sunagawa, M.; Ohta, T.; Nozoe, S. *J. Antibiot.* **1983**, *36*, 25. (c) Yamamoto, Y.; Hori, A.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1985**, *107*, 2471. (d) De La Parra, M. G.; Hutchinson, C. R. *J. Antibiot.* **1987**, *40*, 1170.

(3) (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. Recently, the importance of catalytic quantities of late transition metals has been discovered, see: (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. For intramolecular ring closures of allyl halides and aldehydes with $CrCl_2$, see: (d) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785. (e) Shibuya, H.; Kawashima, K.; Hori, K.; Murakami, N.; Kitagawa, I. *Chem. Lett.* **1986**, 85.

(4) Preparation of oxazolidines: (a) Senkus, M. *J. Am. Chem. Soc.* **1945**, *67*, 1515. (b) Bergmann, E. D.; Gil-Av, E.; Pichas, S. *J. Am. Chem. Soc.* **1953**, *75*, 358. For related use of chiral organotin enamines derived from amino alcohols in addition reactions to unsaturated alkenes, see: (c) deJeso, B.; Pommier, J.-C. *Tetrahedron Lett.* **1980**, 4511. (d) Stetin, C.; deJeso, B.; Pommier, J.-C. *J. Org. Chem.* **1985**, *50*, 3863.

(5) Agami, C.; Rizk, T. *Tetrahedron Lett.* **1985**, *41*, 537.

(6) Similar analysis of the trans (about the oxazolidine ring) isomer leads to the same expectation; note the "pseudo" C_2 symmetry in this case. For the use of chiral enamines derived from C_2 symmetric amines in enantioselective alkylation reactions, see: Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663.

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