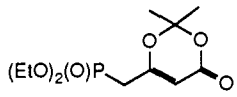
of the trans unsaturated ketene precursor was then effected by Horner–Emmons reaction of **3** with dioxinone phosphonate **7** which afforded exclusively the required *E* unsaturated dioxinone **8** in 65% yield.[10]

The required *Z* olefinic side chain was then elaborated via a cis selective Horner–Emmons reaction[11] of the aldehyde obtained by mild hydrolysis of **8**[12] with allyl bis-trifluoroethylphosphonoacetate **9** providing the *Z* allyl ester **10** (19:1 *Z*/*E*).[13] Deprotection of allyl ester **10** with $Pd(PPh_3)_4$ (catalytic) and NH_4OAc then afforded acid **11** with no detectable double bond isomerization (78% overall from **8**).[14]



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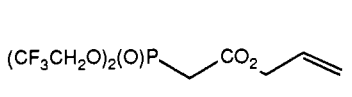

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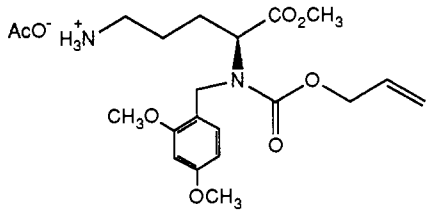

12

The crucial coupling of acid **11** and the primary amine derived from ammonium salt **12**,[15] which proved to be remarkably sensitive to reaction conditions, was realized via addition of **12** to the mixed mesitylene sulfonic anhydride derived from **11** and subsequent treatment with DMAP providing allyl carbamate **13** (60–80% yield),[16,17] Deblocking of **13** ($Pd(PPh_3)_4$ (catalytic)/HOAc) to secondary amine **14** (95%) has now set the stage for formation of the macrocyclic lactam.[14]

As hoped, heating a dilute solution of **14** in $PhCH_3$ (10^{-2}–10^{-4} M) at 105 °C for 8–10 h cleanly provided the macrocyclic bis-amide **15** (~80% yield) via intramolecular trapping of the resulting highly electrophilic acyl ketene.[18]

Transannular Dieckmann cyclization of the highly constrained bis-amide **15** proceeded with noteworthy facility employing standard conditions (*t*-BuOK/*t*-BuOH) affording the penultimate intermediate *N*-(2,4-dimethoxybenzyl)ikarugamycin (**16**) in 75% yield.[19] Deprotection of **16** was then achieved by brief heating of a solution of **16** in anhydrous TFA (0.01 M) at 72 °C providing synthetic (+)-ikarugamycin (**1**) in 55% yield which was chromatographically and spectroscopically indistinguishable from natural (+)-**1**.[20–22]

The foregoing total synthesis confirms both the structure and absolute stereochemistry previously assigned to (+)-ikarugamycin (**1**) by Ito and Hirata.[2] The sequence for conversion of (+)-**2** to (+)-ikarugamycin (**1**) proceeds in about 12 steps. Overall, (+)-ikarugamycin (**1**) is available in about 28 steps (longest linear sequence) from L-glyceraldehyde acetonide.

Acknowledgment. We are extremely grateful to the National Cancer Institute (NCI) of the National Institutes of Health for a grant (CA-29108) in support of these studies. We also thank the University of Rochester for support in the form of a Sherman–Clarke Fellowship to C.H.W.

Supplementary Material Available: ^1H NMR spectra for compounds **1** (synthetic and natural) and intermediates **2–6**, **8**, and **10–16** (15 pages). Ordering information is given on any current masthead page.

(8) Czernecki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699.
(9) For an example of a similar epimerization, see: Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265.
(10) Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823. Boeckman, R. K., Jr.; Perni, R. B.; McDonald, J. E.; Thomas, A. J. *Org. Synth.* **1987**, *66*, 194.
(11) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(12) Coppola, G. M. *Synthesis* **1984**, *12*, 1021.
(13) A variant of the Still procedure[11] was employed to prepare **9** (35% overall yield) from ethyl diethylphosphonoacetate: (a) KOH (1 equiv), CH_3CH_2OH, 25 °C, 16 h; (b) $CH_2{=}CHCH_2Br$ (2 equiv), DMF, 25 °C, 24 h; (c) PCl_5 (2.2 equiv), 75 °C, 3 h; CF_3CH_2OH (2.1 equiv), $(i\text{-}Pr)_2EtN$ (2.1 equiv), PhH, 25 °C, 12 h.
(14) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, *20*, 613. Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.
(15) Ammonium salt **12** was synthesized from L-ornithine·HCl (29% overall yield) via the five-step sequence: (a) $CuCO_3$ (1.4 equiv), H_2O, 100 °C, 1 h followed by $Cl_3CC(CH_3)_2OCOCl$ (1.2 equiv) $NaHCO_3$, H_2O, 25 °C, 24 h then H_2S(g); (b) *t*-$BuOCO_2N{=}C(C_6H_5)CN$ (1.2 equiv), Et_3N (1.5 equiv), dioxane–H_2O (1:1 (v/v)), 25 °C, 24 h; (c) CH_2N_2 (1.1 equiv), Et_2O, 0 °C, 0.5 h; (d) TFA–CH_2Cl_2 (1:5 (v/v)), 0 °C, 1 h; (e) 2,4-$(CH_3O)_2PhCHO$ (1 equiv), $PhCH_3$, then evaporate (<0.5 mm) followed by $NaCNBH_3$ (2 equiv), CH_3OH, 25 °C, 1 h; (f) $CH_2{=}CHCH_2OCOCl$ (2 equiv), DMAP (2 equiv), $ClCH_2CH_2Cl$, 70 °C, 24 h; (g) Zn (10 equiv), HOAc, 25 °C, 2 h.
(16) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.
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(19) Lacey, R. N. *J. Chem. Soc.* **1954**, 850. Use of aprotic solvents for formation of **16** and related tetramic acids is distinctly inferior to *t*-BuOH both in terms of yield and production of pure products.
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(21) Natural (+)-**1**: mp 228–229 °C (CH_3OH), λ_{max} 229, 323 nm, $[\alpha]_D^{25}$ + 360° (*c* 0.19 DMF), α_D^{23} + 289° (*c* 0.12, THF), R_f (silicic acid (Biosil A)) $CHCl_3$–CH_3OH (9:1)), 0.3–0.5 R_f (SiO_2-G, (E. Merck)) EtOH–CH_3CO_2H (4:1)), 0.56.[2] Synthetic (+)-**1**: mp 224–226 °C (CH_3OH), mmp 224–226 °C, λ_{max} 229, 323 nm, $[\alpha]_D^{23}$ + 271° (*c* 0.10, THF), R_f (silicic acid (Biosil A), $CHCl_3$–CH_3OH (9:1)), 0.3–0.5, R_f (SiO_2-G (E. Merck), EtOH–CH_3CO_2H (4:1)), 0.56.
(22) We thank Fujisawa Pharmaceutical Co. Ltd., Higashiyodogawa-ku, Osaka, Japan for an authentic sample of natural (+)-ikarugamycin (**1**) for comparison with synthetic material.

A Triply Convergent Enantioselective Total Synthesis of (+)-Ikarugamycin

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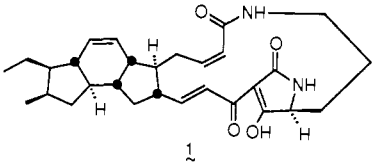
The isolation in 1972 of (+)-ikarugamycin (**1**),[2] an antibiotic possessing antiprotozoal, antiamoebic, and gram-positive activity, was followed quickly by its characterization as a structurally unusual macrocyclic lactam embodying both an enoyltetramic acid



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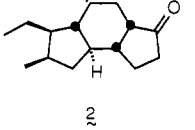

2

moiety and a *trans,anti,cis*-decahydro-*as*-indacene subunit.[3] The challenge surrounding construction and proper amalgamation of

(1) NSERC Postdoctoral Fellow, 1987–1989.
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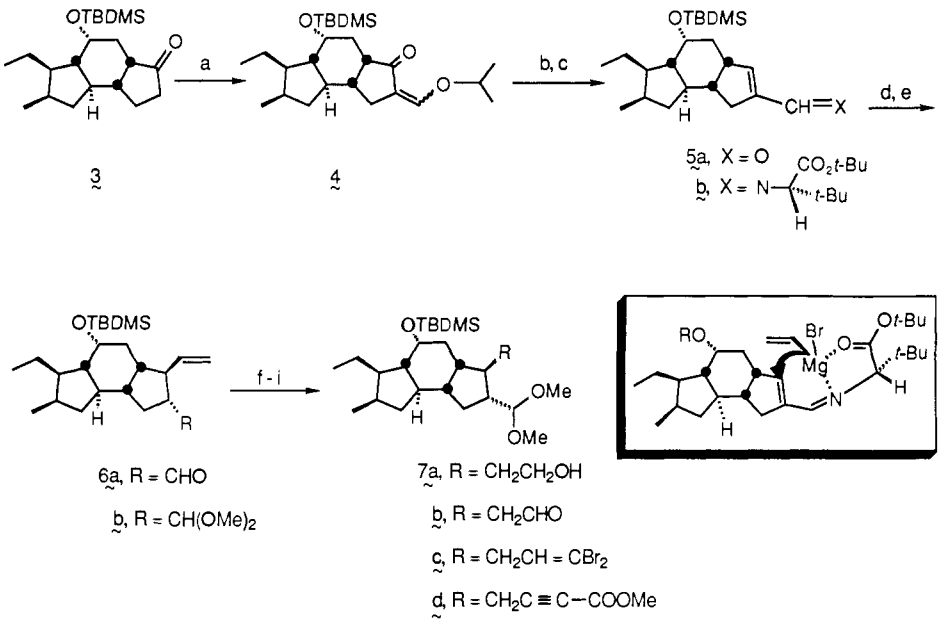
Scheme I[a]

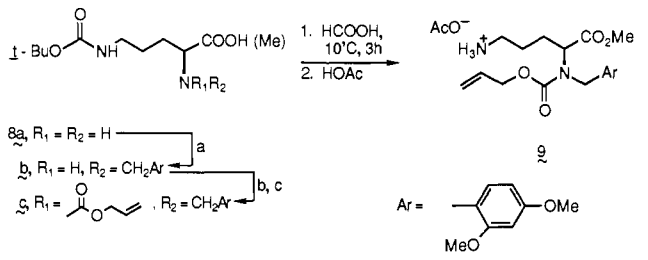


[a](a) $KN(TMS)_2$, THF; HCO_2Et; $(CH_3)_2CHI$, HMPA; (b) Dibal-H, CH_2Cl_2; H_3O^+; (c) L-*tert*-leucine *tert*-butyl ester, ether, (HOAc), $MgSO_4$; (d) CH_2=$CHMgBr$, THF; H_3O^+; (e) $HC(OMe)_3$, (TsOH); (f) Disiamylborane, THF; H_2O_2, NaOH, H_2O; (g) PCC, NaOAc, CH_2Cl_2; (h) CBr_4, PPh_3, CH_2Cl_2; pyridine (workup); (i) *n*-BuLi, THF; $ClCO_2Me$.

these building blocks has recently caused considerable attention to be paid to the possible total synthesis of **1**.[4,5] Recently, we described an expedient route to racemic tricyclic hydroxy ketone **2** in six short steps from (±)-7,7-dimethoxy-5-norbornen-2-one.[5] Herein, we report the successful elaboration of **1** from **2** in an enantioselective manner, The target has been reached in optically active condition as the result of kinetic resolution achieved by suitable application of Koga's chiral α,β-unsaturated aldimine methodology.[6]

The strongly acidic nature of tetramic acids and their customarily low solubility in organic solvents prompted us to approach the target in a manner that would delay assembly of the smaller heterocyclic ring as long as possible, This tactic was additionally attractive because it allowed as well for stereocontrolled and enantioselective attachment of the necessary pendant groups to be accomplished preliminarily. At the outset, **3** was transformed in a one-pot procedure to **4** (67%, Scheme I).[7] Reduction and acidic hydrolysis of **4** made available unsaturated aldehyde **5a** (72%) and set the stage for conversion to aldimine **5b** through condensation with L-*tert*-leucine *tert*-butyl ester.[6] In view of the absolute configuration of the amino acid, the ensuing 1,4-addition of vinylmagnesium bromide was expected to proceed predominantly from the less sterically hindered π face more distal from the *tert*-butyl group in the "matched" diastereomer (see box).[6,8] Additionally, the competing process for introduction of an α-vinyl group should be kinetically disfavored by the concave topography in the vicinity of the β,γ double bond in the "mismatched" diastereomer.

Scheme II[a]



[a](a) ArCHO, $NaBH_3CN$, MeOH; (b) $ClCO_2CH_2CH$=CH_2, $NaHCO_3$, dioxane, H_2O; MeOH; H_3O^+; (c) CH_2N_2.

At the experimental level, **6a** and its isomer were obtained as an inseparable 83:17 mixture with 58% efficiency from **5a**, The enantiomeric purity of **6a** was ascertained as 91% ee following ketalization (97%), hydroboration–oxidation (87%), chromatographic separation of the major primary alcohol **17a** (capable of recrystallization to 98% ee from petroleum ether), and ^{19}F NMR analysis of its Mosher ester.[9] At this point, all eight of the stereogenic centers present in the carbotricyclic segment of ikarugamycin have been set in their proper absolute configuration. Chain lengthening to permit arrival at acetylenic ester **7d** was achieved with exceptional efficiency by known methodology (84% for the three steps).[4a,10]

The appropriate ornithine segment was next assembled by converting the known[4a] γN-*t*-Boc protected amino acid **8a** to the fully protected derivative **8c**, When treated with formic acid at 10 °C, the γ-amino group in **8c** was chemoselectively unmasked (Scheme II), This route to **9** provides for efficient blocking of the α-amino substituent (58% overall). As recognized by others,[4a] deferral of introduction of the CH_2Ar group to a later stage results in a considerably lower yield.

Coupling of **7d** with **9** was accomplished as in a model study[4a] by conversion to a mixed carboxylic–sulfonic anhydride and formation of the amide bond in the presence of 4-(Me_2N)pyridine

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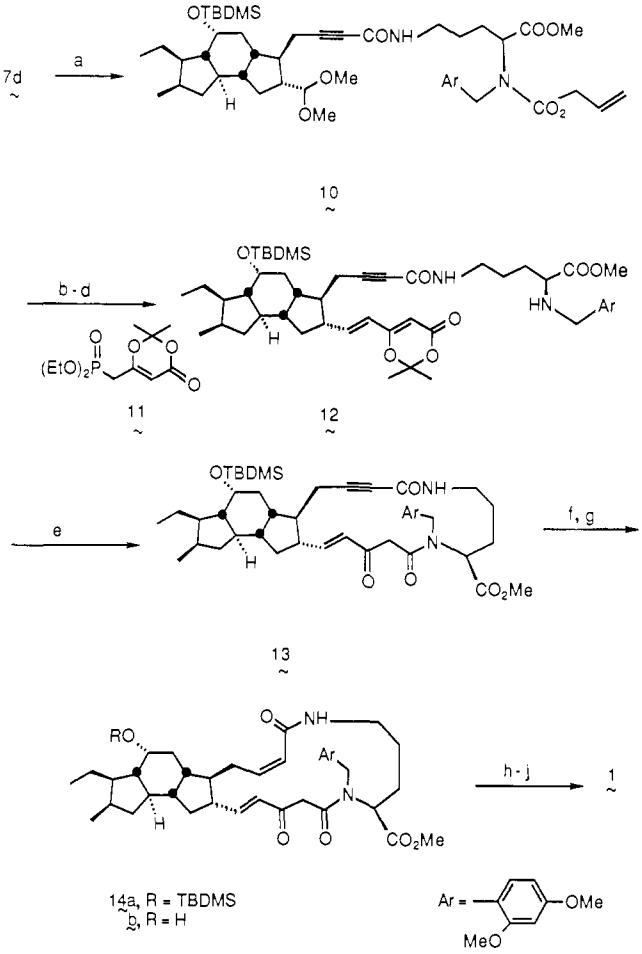
Scheme III[a]



[a] (a) K_2CO_3, MeOH, H_2O; 2,4,6-$(CH_3)_3PhSO_2Cl$, THF; DMAP, **9**; (b) acetone, (TsOH); (c) $KN(TMS)_2$, **11**, THF; (d) $Pd(PPh_3)_4$, PPh_3, HOAc, THF; (e) toluene, 110 °C, 4 h; (f) H_2 (1 atm), 5% Pd–$BaSO_4$, quinoline; (g) 48% HF, CH_3CN; (h) $CH_3OC(O)NSO_2NEt_3$, C_6H_6, Δ; (i) *t*-BuOK (1 equiv), *t*-BuOH; (j) CF_3CO_2H, 65 °C, 10 min.

(58%, Scheme III). Transketalization with dry acetone, conditions found necessary to avoid concomitant deblocking of the silyl ether functionality, made possible condensation with phosphonate **11**[11] and ensuing cleavage of the allyl carbamate under mild conditions [catalytic $(Ph_3P)_4Pd$[12] in the presence of HOAc;[13] THF solution]. Heating dilute solutions of **12** in boiling toluene for 4 h liberated the acyl ketene and induced smooth macrocyclization (65% from **10**). Semisaturation of the acetylenic double bond was next achieved by the Lindlar method (76%). Successive desilylation with 48% hydrofluoric acid (85%) and dehydration of **14b** with the Burgess reagent[14] (40%) proceeded to introduce the requisite B ring double bond.[5]

Completion of the total synthesis was realized by Dieckman cyclization in *t*-BuOH containing 1 equiv of *t*-BuOK[4a] (70%) followed by CF_3COOH-promoted removal of the 2,4-$(MeO)_2$-benzyl group (45%).[15] The IR and ^1H NMR spectra of the synthetic material were identical with those recorded for the natural product.[3,16]

With completion of this convergent and stereoselective route to (+)-ikarugamycin, the focus of attention may perhaps be directed to the preparation of capsimycin, a related natural tetramic acid of some note.[17]

Acknowledgment. We thank the National Institutes of Health for financial support (Grant GM-28468). A helpful exchange of information with Professor R. K. Boeckman, Jr. and his willingness to publish his results simultaneously[18] are deeply appreciated. Professor A. I. Meyers (Colorado State Univ.) as well as Drs. K. Drauz and H. Lotter (Degussa) have made generous samples of L-*tert*-leucine available.

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(13) The presence of acetic acid was necessary to preclude nucleophilic attack by the liberated allylamine on the reaction product.

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(16) This sample was graciously provided us by Professor Boeckman.

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(18) Boeckman, R. K.; Weidner, C. H.; Perni, R. B.; Napier, J. J., preceding paper in this issue.

Total Synthesis of Natural (−)-Echinosporin, Determination of the Absolute Configuration

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Received June 1, 1989

In 1981 Hirayama and co-workers[1] reported the isolation and characterization of echinosporin (**1**), a new antibiotic–antitumor agent produced by *Streptomyces echinosporus* MK-213.[2] The novel, highly oxygenated tricyclic structure, initially deduced by chemical derivatization and NMR analysis, was later confirmed by single-crystal X-ray analysis;[3] however, the absolute configuration remained undefined. Intrigued by the unique tricyclic skeleton, we initiated a program directed toward the enantioselective total synthesis of **1**. Given the unknown absolute stereochemistry, a unified strategy leading to both enantiomers was considered highly desirable (vide infra). Herein we disclose the first total synthesis of natural (−)-echinosporin.[4]

From the retrosynthetic perspective, lactol **2** appeared to be an ideal penultimate intermediate. Of concern here were the three contiguous stereocenters which punctuate the cyclopentene ring. Two of these were anticipated to arise via a [2 + 2] photocycloaddition of cyclopentenone (**5**) to dihydrofuran **6**.[5] Elaboration of the functionality at C(8) in **4** would then involve a palladium-catalyzed carbomethoxylation of the derived enol triflate,[6] followed by a stereocontrolled deconjugative α-hydroxylation. Removal of the acetonide, oxidation of the diol, and ammonolysis of the resultant α-ketolactone (i.e., **3**) were then

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(4) For related synthetic studies, see: Taschner, M. J.; Rach, N. L. Presented at the 190th National Meeting of the American Chemical Society, Chicago, IL, Sept. 8, 1985; ORGN 97. Also, see: Taschner, M. J.; Smith, J. C.; Rach, N. L. 21st Midwestern Regional Meeting of the American Chemical Society, Cleveland, OH, June 2, 1989; ORGN 295. Deprez, D.; Margraff, R.; Bizot, J.; Pulicani, J. P. *Tetrahedron Lett.* **1987**, *28*, 4679.

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