An Enantioselective and Highly Convergent Synthesis of (+)-Ikarugamycin

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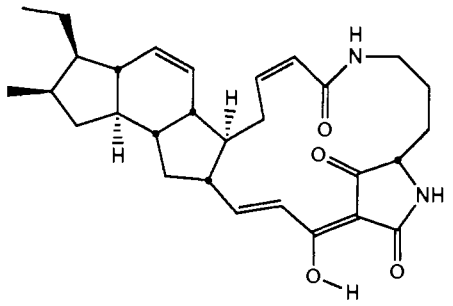
(+)-Ikarugamycin (**1**), the initial member of a novel class of macrocyclic lactam tetramic acid antibiotics possessing a range of biological activity, was isolated in 1972.[1] The structure and absolute stereochemistry of **1** was assigned in 1976 employing a combination of chemical degradation and spectroscopic methods.[2] A retrosynthetic analysis of **1** led to the identification of tetracyclic ketone **2** as a key intermediate. A convergent, highly stereoselective synthesis of (+)-**2** was developed in our laboratories employing a key intramolecular Diels–Alder reaction to assemble the required *as*-hydrindacene nucleus.[3] An efficient, convergent solution to the formidable challenge presented by the tetramic acid-containing macrocyclic lactam subunit of **1** was also devised in our laboratories utilizing a new ketene-mediated cyclization for the construction of the 16-membered macrocyclic lactam ring.[4] Herein we describe the application of this strategy to the total synthesis of (+)-**1**.[5]



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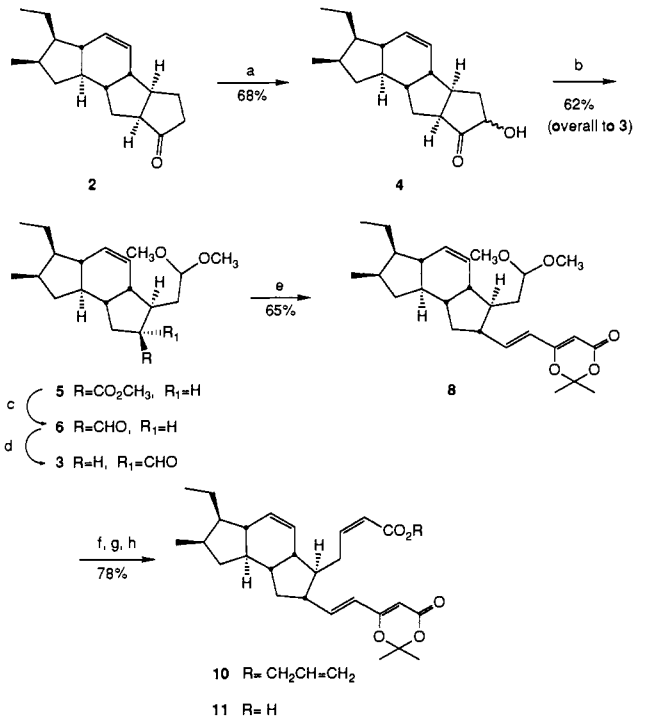
In order to implement the aforementioned sequence to (+)-**1** beginning with (+)-**2**, elaboration of **2** to a differentially protected tricyclic dialdehyde **3** was required to allow the sequential construction of the *E* and *Z* unsaturated carbonyl residues present in **1** (Scheme I). With suitably differentiated appendages in place, coupling of the *Z* unsaturated carbonyl function with an appropriately protected L-ornithine derivative, followed by macrocyclization and formation of the tetramic acid, then completes the conversion to **1**.

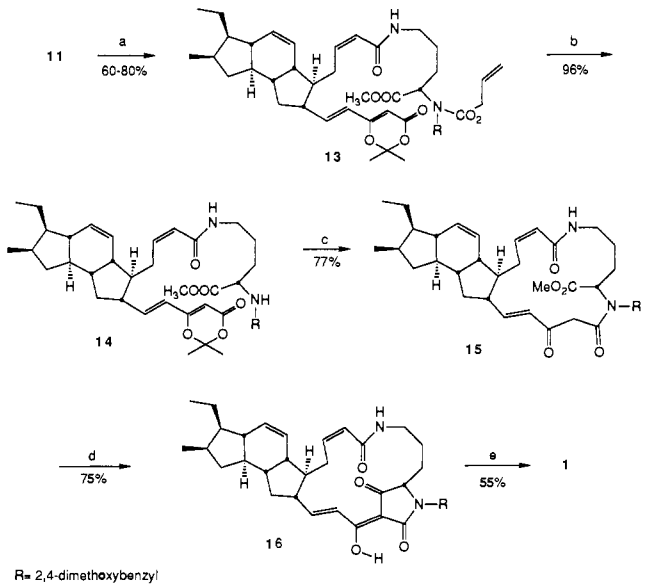
Elaboration of (+)-**2** (mp 65–67 °C, $[\alpha]_D^{25}$ + 103° (*c* 2.8, $CHCl_3$)) was initiated by oxidation with $PhI(OAc)_2$ to afford a mixture of acyloins **4** (4:1 α/β) in 68% yield (Scheme I).[6,7] Subsequent oxidative cleavage of **4** with $Pb(OAc)_4$ in anhydrous CH_3OH and immediate protection of the resulting ester aldehyde cleanly provided ester acetal **5** (90% from **4**). Utilizing standard chemistry, **5** could be converted to aldehyde acetal **6**, which as expected underwent epimerization to the more stable trans aldehyde **3** on exposure to DBU (62% overall from **4**).[8,9] Installation

Scheme I[a]



[a] Reagents: (a) $PhI(OAc)_2$ (1.2 equiv), KOH (2 equiv), CH_3OH, 25 °C, 8 h then Amberlyst-15, THF–H_2O (95:5 (v/v)), 25 °C, 24 h; (b) $Pb(OAc)_4$ (1.05 equiv), CH_3OH–THF (1:1 (v/v)), 0 °C, 0.5 h then Amberlyst-15, 3Å molecular sieves, CH_3OH, 25 °C, 16 h; (c) Di-BAL-H (2 equiv), THF, 0 °C, 2 h; (d) PDC (2 equiv), 3Å molecular sieves, CH_2Cl_2, 25 °C, 0.5 h, then DBU (catalytic), CH_2Cl_2, 0 °C, 72–120 h; (e) **7** (1.2 equiv), KHMDS (1.2 equiv), THF, 0 °C → 25 °C, 4 h; (f) Amberlyst-15, CH_3CN–H_2O (9:1 (v/v)), 25 °C, 12 h; (g) **9** (1 equiv), K_2CO_3 (6 equiv), 18-c-6 (10 equiv), $PhCH_3$, −20 °C → 0 °C, 4 h; (h) NH_4OAc (4 equiv), $Pd(PPh_3)_4$ (catalytic), dioxane, 25 °C, 24 h.

Scheme II[a]



[a] Reagents: (a) mesitylene sulfonyl chloride (1 equiv), Et_3N (1 equiv), THF, 25 °C, 10 min then **12** (2–3 equiv), DMAP (3–4 equiv), THF, 25 °C, 4 h; (b) HOAc (xs), $Pd(PPh_3)_4$ (catalytic), THF, 25 °C, 12 h; (c) $PhCH_3$, 105 °C, 8–10 h; (d) *t*-BuOK (2 equiv), *t*-BuOH, 0 °C, 15 min; (e) anhydrous TFA (0.01 M in substrate), 72 °C, 5 min.

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

(2) Ito, S.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1813.

(3) Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152. For other approaches to the carbocyclic system of **1**, see: Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 6403 and references therein.

(4) For a discussion of the various synthetic strategies for formation of the macrocyclic ring, see: Boeckman, R. K., Jr.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486.

(5) See the following paper in this issue for an alternative total synthesis of (+)-**1** by Paquette and co-workers: Paquette, L. A.; Macdonald, D.; Anderson, L.; Wright, J. *J. Am. Chem. Soc.* **1989**, *111*, following paper in this issue.

(6) All new substances exhibited satisfactory spectroscopic (NMR, IR, UV) and combustion or high-resolution mass spectral analytical data.

(7) Moriarity, R. M.; Hou, K. C. *Tetrahedron Lett.* **1984**, *25*, 691. Use of highly electrophilic oxidants was precluded by the unexpectedly high reactivity of the strained double bond in **2**.

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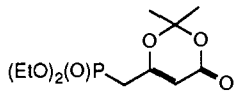
of the trans unsaturated ketene precursor was then effected by Horner-Emmons reaction of **3** with dioxinone phosphonate **7** which afforded exclusively the required *E* unsaturated dioxinone **8** in 65% yield.[10]

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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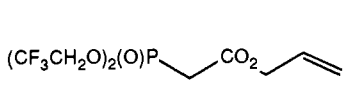

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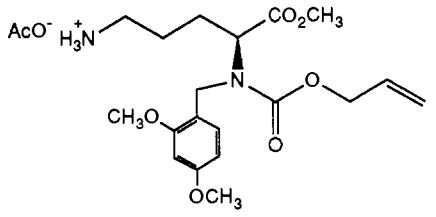

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The crucial coupling of acid **11** and the primary amine derived from ammonium salt **12**,[15] which proved to be remarkably sensitive to reaction conditions, was realized via addition of **12** to the mixed mesitylene sulfonic anhydride derived 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.
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(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.
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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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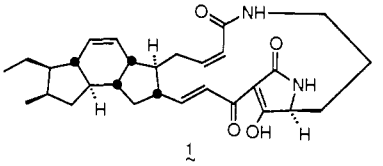
The isolation in 1972 of (+)-ikarugamycin (**1**),[2] an antibiotic possessing antiprotozoal, antiamoebic, and gram-positive activity, was followed quickly by its characterization as a structurally unusual macrocyclic lactam embodying both an enoyltetramic acid



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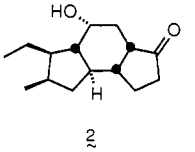

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moiety and a *trans,anti,cis*-decahydro-*as*-indacene subunit.[3] The challenge surrounding construction and proper amalgamation of

(1) NSERC Postdoctoral Fellow, 1987-1989.
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