Application of η^4-Diene Iron Tricarbonyl Complexes in Acyclic Stereocontrol: Asymmetric Synthesis of the *as*-Indacene Unit of Ikarugamycin (A Formal Total Synthesis)

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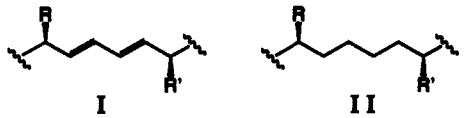
Received November 17, 1993

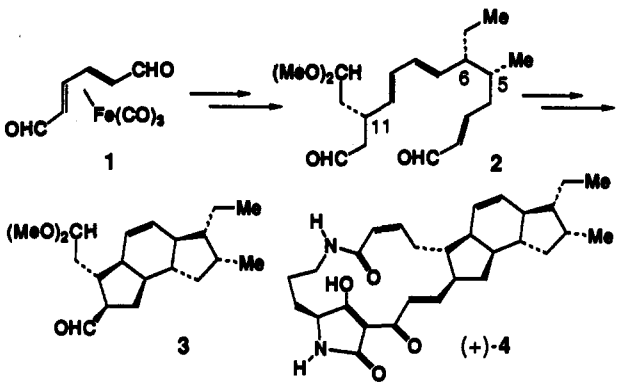
While numerous strategies exist for 1,2- 1,3- and 1,4-asymmetric induction,[1,2] control of more remote relationships continues to be a challenging problem in organic synthesis.[3] This problem is further compounded when the remote stereogenic centers involve alkyl branching, as in structures **I** and **II**. Classically, such structures would be synthesized by the coupling of two smaller fragments at a nonstereogenic center.



I **II**

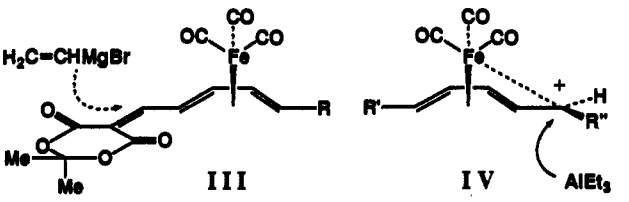
We report herein a conceptually new solution to the problem of 1,6-asymmetric induction defined by **I**, involving three highly enantio- and diastereoselective transformations of *meso*-(η^4-2,4-hexadien-1,6-dial)iron tricarbonyl, **1**. This procedure is illustrated by the stereocontrolled synthesis of triene **2**, an intermediate that we have elaborated into the *as*-indacene nucleus **3** of ikarugamycin, **4**.[4] Since Boeckman has already described the conversion of **3** into ikarugamycin,[5] our asymmetric synthesis of **3** constitutes a formal total synthesis of the natural product.[6,7]

The starting point for these investigations was our observation that the asymmetric allylboration of **1** proceeds with exceptional diastereo- and enantioselectivity.[8] Similarly, the asymmetric (*E*)-crotylboration of **1** using 0.95 equiv of (*S,S*)-**5** in toluene at –78 °C[9] provided the Ψ-exo diastereomer **6** in 90% yield and ≥98% ee. This reaction sets the C(5)–Me stereocenter of **2**, introduces a diene allylic alcohol function that is suitable for subsequent elaboration into the C(6)–Et substituent,[10,11] and provides a third



stereogenic unit in the form of the η^4-diene $Fe(CO)_3$ complex that is used to induce the C(11) stereocenter of **2**. The latter problem was addressed first.

Condensation of **6** with 1.0 equiv of Meldrum's acid gave **7** in 92% yield. Treatment of **7** with 2.5 equiv of $H_2C{=}CHMgBr$ in THF at –78 °C with warming to 0 °C then provided the 1,4-adduct **8** in 83% yield as the only observed stereoisomer (≥97:3 by 500-MHz ^1H NMR analysis).[12] The stereochemical course of this reaction is rationalized by **III**, in which $H_2C{=}CHMgBr$ adds to the bottom face of the alkylidene malonate, away from the -$Fe(CO)_3$ unit that blocks the top face.[11,12] Acylation of **8**



III **IV**

under standard conditions provided **9**, which was then treated with 2.0 equiv of Et_3Al in CH_2Cl_2 at –20 °C to 0 °C.[10] This provided **10** as the sole product in 69–75% overall yield. That the alkylation of **9** proceeds with retention of configuration, evidently with the -$Fe(CO)_3$ unit assisting in the departure of the acetate leaving group and Et_3Al adding to the -$Fe(CO)_3$-stabilized carbocation from the exo face as illustrated in **IV**,[10,11,13] was verified by the further conversion of **10** to the ikarugamycin subunit **3**. Lillya established years ago that solvolysis of Fe-$(CO)_3$-complexed dienylic dinitrobenzoates proceeds with retention of configuration,[13] and more recently Uemura and co-workers developed the alkylation of $Fe(CO)_3$-complexed dienylic acetates with soft carbon nucleophiles.[10] However, to the best of our knowledge, the elaboration of **10** to **3** provides the first experimental evidence that such C-alkylations also proceed with retention of configuration.

The -$Fe(CO)_3$ unit was removed by treatment of **10** with $FeCl_3$.[11] Hydrolysis of the resulting uncomplexed diene with H_2O in 3-pentanone at reflux followed by CH_2N_2 esterification provided methyl ester **11** in 70% overall yield.[12] Hydroboration of both vinyl groups was performed by treating **11** with 3.0 equiv of 9-BBN. The two primary alcohols were then differentiated by cyclization of the δ-hydroxy ester to a δ-lactone upon exposure of the diol ester to PPTs in toluene at 80 °C. Finally, Swern oxidation[14] of the remaining primary alcohol provided lactone aldehyde **12** in 57–60% overall yield. Triene dialdehyde **2** was then obtained in 56% overall yield from **12** via the series of standard functional group manipulations summarized in Scheme 1.[15]

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(3) Selected recent examples of 1,*n*-asymmetric induction ($n > 4$): (a) Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984. (b) Ferreira, J. T. B.; Simonelli, F. *Tetrahedron* **1990**, *46*, 6311. (c) Tamai, Y.; Koike, S.; Ogura, A.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1991**, 799. (d) Shimizu, M.; Mikami, K. *J. Org. Chem.* **1992**, *57*, 6105. (e) Molander, G. A.; Bobbitt, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 7517. (f) Carey, J. S.; Thomas, E. J. *Tetrahedron Lett.* **1993**, *34*, 3935.

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(5) Boeckman, R. K., Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036.

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(7) For other studies on the synthesis of ikarugamycin: (a) Kurth, M. J.; Burns, D. H.; O'Brien, M. J. *J. Org. Chem.* **1984**, *49*, 731. (b) Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 6403. (c) Jones, R. C. F.; Jones, R. F. *Tetrahedron Lett.* **1990**, *31*, 3363, 3367.

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(15) (a) HWE: Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

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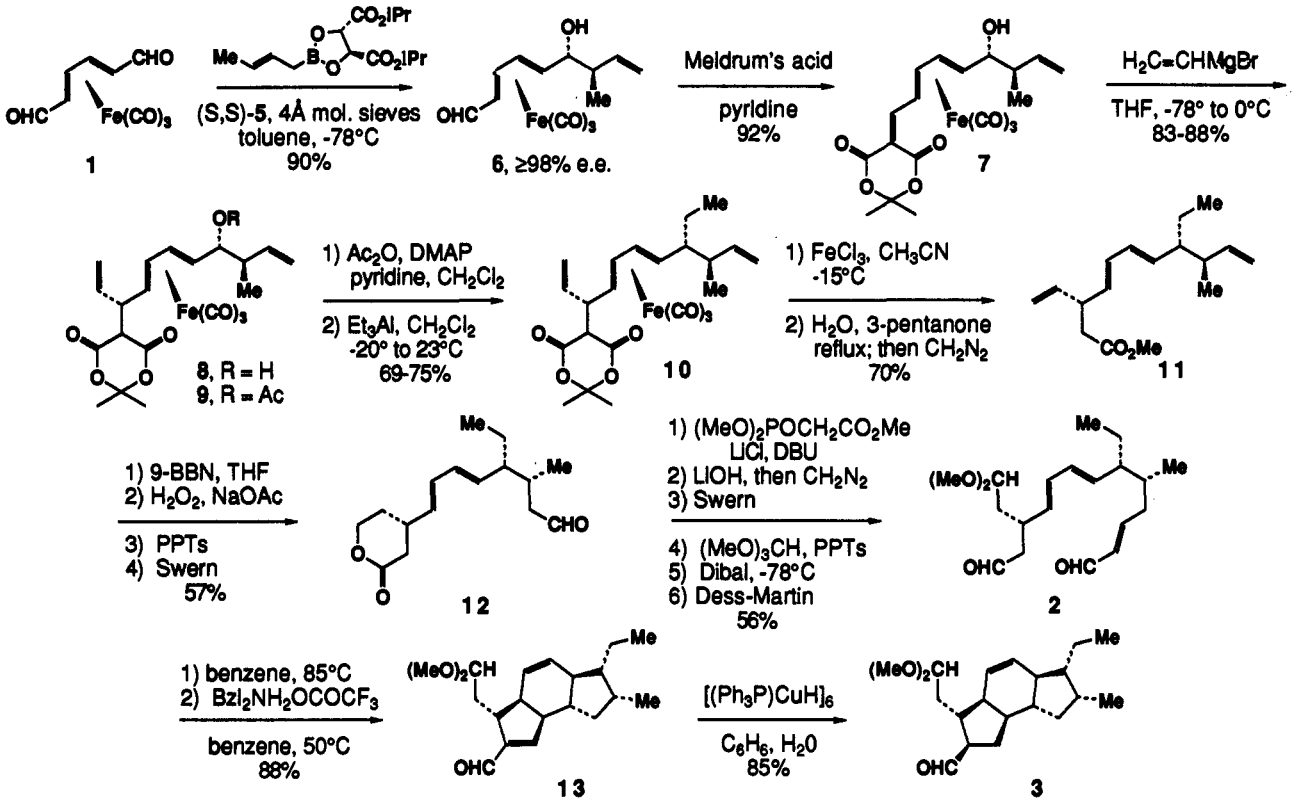
Scheme 1



The intramolecular Diels–Alder reaction of **2** (C_6H_6, 85 °C, 82 h)[16] provided a 12:1 mixture of cycloadducts which, without separation, was directly cyclized to enal **13** upon treatment with $Bzl_2NH_2^+CF_3CO_2^-$ in C_6H_6 at 50 °C.[17] This provided diastereomerically pure **13** in 88% overall yield. Finally, reduction of **13** with $[(Ph_3P)CuH]_6$ in wet benzene[18] provided the ikarugamycin *as*-indacene nucleus **3** ($[\alpha]^{20}_D$ +21.2° (c = 0.81, $CHCl_3$); lit.[19] $[\alpha]^{20}_D$ +12.3° (c = 0.71, $CHCl_3$)) in 85% yield as a 9:1 mixture of aldehyde epimers. The ^1H NMR data obtained for **3** and the aldehyde epimer are in complete agreement with the NMR spectra of authentic samples kindly provided by Professor R. K. Boeckman, thereby completing the formal total synthesis.

Acknowledgment. This research was supported by the National Institute of General Medical Sciences (GM 38907). C.K.W. gratefully acknowledges fellowships provided by Procter and Gamble and the Department of Education. We also thank Dr. J. C. Park for performing the first asymmetric crotylborations of **1**.

Supplementary Material Available: Experimental procedures and full characterization data for **6-13**, **2**, and **3** (19 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(19) We thank Professor Boeckman for providing us with optical rotation data and copies of the ^1H NMR spectra of **3** and the aldehyde epimer.