ployed. This has been done with (*E*)-α-phenylcinnamyl alcohol, geraniol, and *trans*-2-decen-1-ol. All give normal face selection (i.e., 2*S* with (+)-DET) to the extent of 78, 70, and 65% ee, respectively. We cannot yet explain why the normal enantioselection is preserved to such a high degree in these reactions.

Many questions remain to be answered about these epoxidation catalysts in both the 2:1 and 2:2 systems. Kinetic studies of these processes are under way, and we are increasing our efforts to obtain crystalline derivatives for X-ray structural analysis.

These new 2:1 inverse induction systems are already useful in special cases,[17] and, if the enantioselectivities can be further enhanced, they could become truly valuable additions to the already popular parent asymmetric epoxidation process.

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM28384), Eli Lilly and Company, and Exxon Chemical Company. We also acknowledge the excellent assistance of Mr. Jonathan Ellman in the preparation and characterization of ligand **5e**, as well as the MIT undergraduate research opportunities program for his financial support.

Supplementary Material Available: Results of epoxidations mediated by tartrate amide derivatives and other chiral ligands (45 ligands in all); preparation and properties of ligand **5e**; experimental details of chlorohydroxylation reactions (16 pages). Ordering information is given on any current masthead page.

(17) The chlorohydroxylation system is probably the most useful as it allows asymmetric oxidation of certain sensitive substrates (e.g. **9**, see also ref 8) that are either very poor or fail completely in the standard asymmetric epoxidation process. For research purposes the 2:1 tartramide system is clearly inferior to the standard system because it is less enantioselective. However, in a commercial application it could prove superior to the normal catalyst in cases where the substrate is favorable and the required enantioselection is that based on use of the unnatural tartrate ester in the standard asymmetric epoxidation process.

(18) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240. (b) Katsuki, T.; Sharpless, K. B. *Ibid.* **1980**, *102*, 5974–5976.

(19) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819–3822.

(20) On sabbatical leave from The Upjohn Company, Kalamazoo, MI, Sept 1, 1982–Aug 31, 1983.

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Ikarugamycin: Total Synthesis of the Decahydro-*as*-indacene Portion

Summary: An efficient, stereoselective synthesis of octahydro-*as*-indacenone **2**, the carbocycle fragment of the antibiotic ikarugamycin, is described. The prominent step in this sequence is an intramolecular Diels–Alder reaction, which establishes the relative stereochemistry of **2**.

Sir: Ikarugamycin (**1**) was isolated in 1972 by Jomon et al.[1] from a culture broth of *Streptomyces phaeochromogens var. ikarugamycin* Sakai and was fully characterized in 1977 by Ito and Hirata.[2] Its biological properties include strong specific antiprotozoal activity, in vitro antiamoebic activity, and activity against some Gram-positive bacteria.[1] Structurally ikarugamycin is a unique natural product that embodies an enoyltetramic acid containing macrocyclic lactam and a rare *trans-anti-cis*-decahydro-*as*-indacene system.[3] These structural features have recently attracted synthetic investigation.[4]

We have undertaken a synthetic approach to ikarugamycin, which at its focal point relies on the intermediacy of octahydro-*as*-indacenone **2**. Our strategy for the synthesis of **2** is outlined retrosynthetically in Scheme I. Key features in this analysis include (a) efficient access to trienoate **4** by rational manipulation of the terminal functionalities of pentenoic acid **5**, (b) a stereoselective intramolecular Diels–Alder reaction yielding tetrahydroindan **3**, and (c) regioselective ring C annulation. Examination of molecular models for the two diastereomeric endo-Diels–Alder transition states of **4** suggested that the steric demands of the vicinal chiral centers in this trienoate would dictate cycloaddition via the sterically preferred transition state A.[5] Subsequent ring C elaboration was envisaged via routes including a Collman carbonyl insertion sequence (**2a**, X = H) and a homologation/condensation sequence (**2b**, X = SO_2Ar). In this report, we describe an efficient procedure that delivers the crucial carbocyle **2** appropriately disposed for elaboration to ikarugamycin.

Our plan for the synthesis of **2** was conjunctive with the ready availability of intramolecular Diels–Alder precursor **4** from pentenoic acid **5**. Thus, **5**,[6] prepared in 83% yield by ester enolate Claisen rearrangement[7] of (*E*)-crotyl butanoate (LDA, THF, −78 °C; Me_3SiCl; −78 → 40 °C; H_3O^+), was reduced with lithium aluminum hydride to the corresponding alcohol (Scheme II). Parikh-modified[8] Moffatt oxidation followed by immediate condensation of the resulting aldehyde with the lithio salt of methyl 4-(diethylphosphono)crotonate at −40 °C in THF furnished the (*E,E*)-triene ester. Diisobutylaluminum hydride reduction afforded trienol **6**[6] in 49% overall yield from acid **5**. Regioselective hydroboration of the *tert*-butyldimethylsilyl ether of **6** with 9-BBN[9] gave as expected the terminal

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

(2) (a) Ito, S.; Hirata, Y. *Bull. Soc. Chem. Jpn.* **1977**, *50*, (a) 227; (b) 1813.

(3) To our knowledge, the only other natural product containing the *trans-anti-cis-as*-hydrindacene system is the related antibiotic capsimycin: Aizawa, S.; Akutsu, H.; Satomi, T.; Nagatsu, T.; Taguchi, R.; Mogami, M.; Komuro, H.; Seino, A. *J. Antibiot.* **1979**, *32*, 193.

(4) (a) Since submission of this manuscript, a stereoselective preparation of a tetracyclic intermediate for ikarugamycin has been reported: Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152. (b) Progress toward the *as*-hydrindacene skeleton of ikarugamycin was recently described: Whitesell, J. K.; Minton, M. A.; Fisher, M. "Abstract of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, Aug 1983, American Chemical Society: Washington, DC: 1983; ORGN 300. (c) A preparation of phosphonate-activated 3-acetyltetramic acids has been reported: Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823.

(5) For related intramolecular Diels–Alder strategies, see: (a) Roush, W. R.; Meyers, A. G. *J. Org. Chem.* **1981**, *46*, 1509. (b) Nicolaou, K. C.; Magolda, R. L. *Ibid.* **1981**, *46*, 1506.

(6) This was an 89:11 erythro:threo mixture, which was difficult to separate. This diastereomeric mixture gave satisfactory IR, NMR, mass spectrometry, and analytical or exact mass data.

(7) Ireland, R.; Mueller, R.; Willard, A. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(8) Parikh, J. R.; Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(9) (a) Brown, H. C.; Knights, E. F.; Coleman, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 2144. (b) Brown, H. C.; Zweifel, G.; Nagase, K. *Ibid.* **1962**, *84*, 183.

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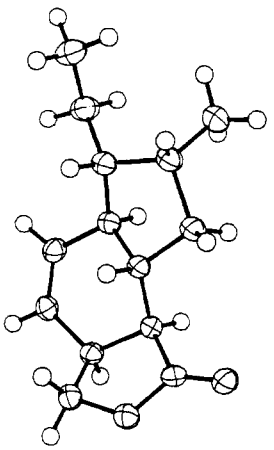


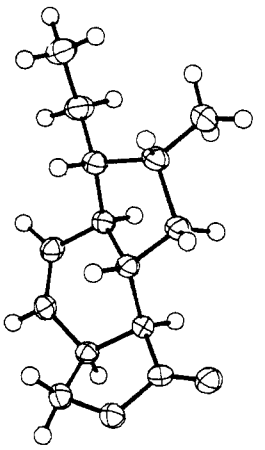
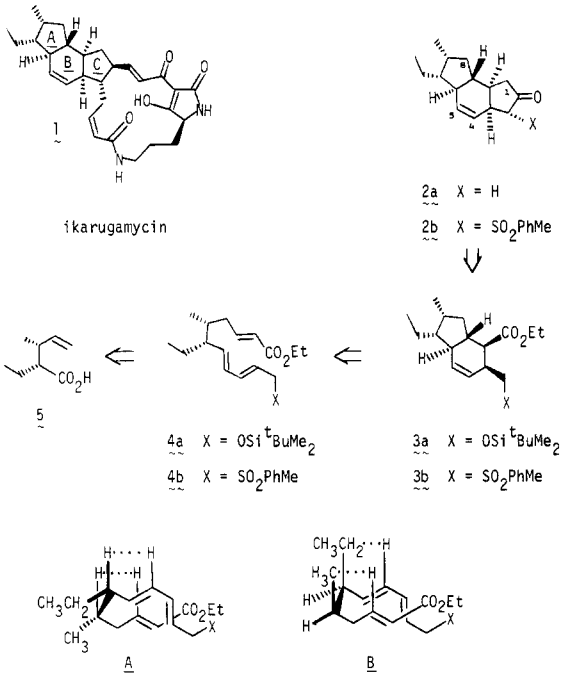
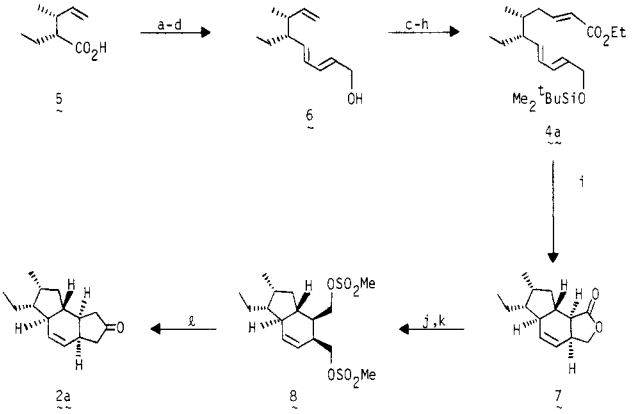


Figure 1. Stereoscopic view of the X-ray structure of 7.

Scheme I



Scheme II[a]



[a] All reactions were carried out under nitrogen. (a) $LiAlH_4$ (6.0 equiv of hydride), Et_2O, 25 °C, 16 h (93%). (b) Pyr·SO_3 (4.0 equiv), TEA (7.0 equiv), Me_2SO, 25 °C, 1.5 h (83%). (c) (*i*) $(EtO)_2P(O)CH_2CH{=}CHCO_2Me$ (1.1 equiv), LDA (1.1 equiv), THF, −78 °C, 30 min; (*ii*) RCHO (1.0 equiv) THF, −40 → 0 °C, 1.5 h (67%). (d) DIBAH (2.2 equiv), CH_2Cl_2, −78 °C, 3 h (94%). (e) Imidazole (2.4 equiv), *t*-BuSiCl (1.2 equiv), DMF, 25 °C, 1.5 h (99%). (f) (*i*) 9-BBN (1.1 equiv), THF, 0-25 °C, 2.2 h; (*ii*) EtOH, NaOH, H_2O, H_2O_2, 50 °C, 1.5 h (80%). (g) PCC (7.0 equiv), NaOAc (1 equiv), CH_2Cl_2, 0 → 25 °C, 2.5 h (97%). (h) (*i*) $(EtO)_2P(O)CH_2CO_2Et$ (2.0 equiv), *t*-BuOK (1.8 equiv), THF, 25 °C, 30 min; (*ii*) RCHO (1.0 equiv), THF, 25 °C, 45 min (61%). (i) (*i*) **4a** in *m*-xylene (0.05 M), degassed, 139 °C, 40 h; (*ii*) 1:3:3 48% aqueous HF/THF/CH_3CN, 25 °C, 1.5 h (55%). (j) $LiAlH_4$ (4.0 equiv of hydride), Et_2O, 25 °C, 4 h (93%). (k) MsCl (4.0 equiv), TEA (5.0 equiv), CH_2Cl_2, 0 °C, 45 min (82%). (l) $Na_2Fe(CO)_4$ (1.2 equiv), Ph_3P (2.0 equiv), 1-methyl-2-pyrrolidinone, 25 °C, 48 h (5%).

alcohol. Finally PCC[10] oxidation followed by Horner–Emmons condensation with the potassium salt of ethyl (diethylphosphono)acetate furnished **4a**[6] in 47% overall yield from trienol **6** and accessed the crucial intramolecular Diels–Alder cycloaddition.

Heating **4a** in degassed *m*-xylene at 139 °C for 40 h afforded **3a**[11] along with two isomers tentatively assigned as the methyl epimer of **3a** (from the threo diastereomer of **4a**) and the exo addition isomer. Treatment of this isomeric mixture[12] with aqueous hydrofluoric acid in THF induced concomitant desilylation/lactonization. Crystalline 7,[11] obtained in 55% overall yield from **4a**, was subjected to single-crystal X-ray diffraction analysis.[13] An ORTEP drawing that confirms the structure of 7 is presented in Figure 1.

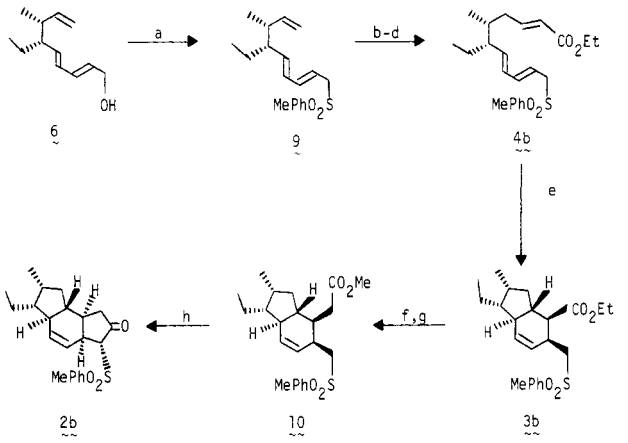
(10) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(11) All new compounds have been fully characterized by IR, ^1H NMR, and mass spectroscopies, and elemental composition has been established by combustion analysis and/or high-resolution mass spectroscopy.

(12) The three isomeric adducts (94% combined yield) were not readily separated by silica gel chromatography. High-field ^1H NMR analysis of this mixture indicated that **3a** was 70–75% of the total. Routine separation was delayed until the lactone stage (**7**).

(13) (a) Compound 7 ($C_{14}H_{20}O_2$) crystallizes from hexane in the monoclinic space group, $P2_1/a$. The crystal data at 140 K are as follows: a = 13.011 (3) Å, b = 4.951 (1) Å, c = 18.545 (4) Å; β = 91.83 (2)°; ρ(calcd) = 1.22 g cm^{-3} for Z = 4; 2θ(max) = 55°; 2100 reflections with $F > 6\alpha(F)$ used, Mo Kα (graphite) (λ = 0.71069 Å), and ω scan, 60° min^{-1}; R = 0.040. SHELXTL programs on a DGC Eclipse S/230 computer. X-ray crystallographic details will be reported elsewhere: Hope, H.; Oram, D. *Acta Crystallogr.*, manuscript submitted. (b) Data for **7**: mp from hexane 78–80 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 6.06 (d, J = 10.1 Hz, 1 H, H-5), 5.57 (dt, J = 10.1, 2.9 Hz, 1 H, H-4), 4.51 (t, J = 8.6 Hz, 1 H, H-3β), 3.88 (dd, J = 10.4, 8.6 Hz, 1 H, H-3α), 3.21 (m, 1 H, H-3a), 2.51 (dd, J = 12.6, 8.6 Hz, 1 H, H-8b), 2.38–2.24 (m, 3 H, H-6, H-7, H-8α), 1.68 (br t, J = 8.8 Hz, 1 H, H-5a), 1.63–1.36 (m, 3 H, H-8a, CH_2-10), 1.07 (m, 1 H, H-8β), 0.96 (t, J = 6.8 Hz, 3 H, CH_3-11), 0.92 (d, J = 6.8 Hz, 3 H, CH_3-9); IR (CCl_4) 3024, 1780 cm^{-1}; mass spectrum, m/e 220.2 (molecular ion). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.10; H, 9.12.

Scheme III[a]



[a] All reactions were carried out under nitrogen. (a) (*i*) MeLi (1.05 equiv), 3:1 Et_2O/HMPA, 0 °C, 30 min; (*ii*) TsCl (1.2 equiv), HMPA, 0 °C, 2.5 h; (*iii*) $MePhSO_2Na \cdot 2H_2O$ (1.2 equiv), DMF, 25 °C, 16 h (88% overall). (b) (*i*) 9-BBN (1.2 equiv), THF, 25 °C, 2.5 h; (*ii*) NaOH, H_2O, H_2O_2, 25 °C, 2.5 h (81%). (c) PCC (8.0 equiv), CH_2Cl_2, 25 °C, 2.5 h (89%). (d) $(EtO)_2P(O)CH_2CO_2Et$, (1.05 equiv), KOH (3.8 equiv), THF, 25 °C, 15 min (71%). (e) **4b** in *m*-xylene (0.05 M), degassed, 139 °C, 32 h (70%). (f) 1:8 6 N aqueous KOH/EtOH, reflux, 2 h (95%). (g) (*i*) $SOCl_2$ (2.0 equiv), pyridine (0.02 equiv), CH_2Cl_2, 25 °C, 4 h; (*ii*) CH_2N_2 (2.5 equiv), 2:1 Et_2O/THF, 0 °C for 30 min and 25 °C for 30 min; (*iii*) Ag_2O (1.6 equiv), MeOH, 64 °C, 2 h (75% overall). (h) NaH (4.0 equiv), THF, 25 °C, 1 h (90%).

With lactone **7** in hand, annulation via a carbonyl insertion procedure was broached. While tetrahydrofuran formation was problematic in the bistosylation of the diol obtained by lithium aluminum hydride reduction of **7**, bismesylation to **8**[11] was well disposed (76% from **7**). Treatment of **8** with disodium tetracarbonylferrate (Collman's reagent)[14] in 1-methyl-2-pyrrolidinone containing triphenylphosphine gave **2a**[11] in disappointingly low yield (5%).[15]

In light of this outcome, a congener was sought which would facilitate ring C formation. An arylsulfone modified Diels–Alder substrate appeared ideal inasmuch as the arylsulfone moiety might (a) accommodate a variety of synthetic manipulations, (b) access condensative ring C formation, and (c) regiospecifically functionalize the incipient octahydro-*as*-indacenone, thus extricating elaboration to ikarugamycin. Scheme III delineates our realization of these objectives.

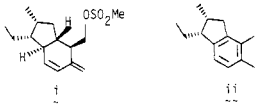
A convenient one-pot tosylation/sulfinate displacement sequence[16] converted **6** to sulfone **9**[6] in 88% yield. The series of reactions described for **6** → **4a** were now repeated on sulfone **9**. Thus, regioselective hydroboration with 9-BBN, PCC oxidation, and finally Horner–Emmons condensation led to **4b**[6] in 52% overall yield from **9**. Diastereoface selective Diels–Alder cycloaddition of **4b** afforded crystalline **3b**[11] in 70% isolated yield. Two minor isomers were obtained in 14% yield.[17] Elaboration of **3b** to **2b** required one carbon ester homologation and was accomplished via a standard Arndt–Eistert procedure.[18] Accordingly, **3b** was saponified and the crude acid converted to the acid chloride. Diazomethane treatment followed by silver oxide promoted Wolff rearrangement in refluxing methanol furnished ester **10**[11] in 72% overall yield from **3b**. Sulfone/ester cyclization was effected with sodium hydride in THF, providing octahydro-*as*-indacenone **2b** as the only isolable product in 90% yield. The stereochemical integrity of **2b**[19] was verified by its desulfurization[20] to **2a**[19] (76%).

The enantioselective preparation of **2** is currently in progress.[21] Further developments stemming from these investigations will be forthcoming.

Acknowledgment is made to the Committee on Research of the University of California, Davis and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. We gratefully acknowledge IBM Instruments for donation of an LC/9533 ternary high-pressure liquid chromatography system.

(14) Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342.

(15) The only other compound isolated was elimination product i[11] (23% from **8**) which readily aromatized to indan ii.



(16) Altman, L. J.; Ash, L.; Marson, S. *Synthesis* **1974**, 129.

(17) While MPLC afforded pure **3b**, the two minor isomers, which are presumed to be the methyl epimer of **3b** and the exo addition isomer, were cross-contaminated.

(18) Boeckman, R. K., Jr.; Sum, F.-W. *J. Am. Chem. Soc.* **1982**, *104*, 4604.

(19) (a) Data for **2a**: ^1H NMR (360 MHz, $CDCl_3$) δ 5.91 (d, *J* = 9.9 Hz, 1 H, H-5), 5.76 (dt, *J* = 9.9, 3.3 Hz, 1 H, H-4), 2.95 (m, 1 H, H-3a), 2.46 (dd, *J* = 18.7, 9.0 Hz, 1 H, H-3), 2.42 (ddd, *J* = 18.5, 8.5, 1.3 Hz, 1 H, H-1), 2.34–2.23 (m, 3 H, H′-1, H-7, H-8b), 2.11 (dt, *J* = 12.6, 7.2, 1 H, H-8α), 1.98 (ddd, *J* = 18.7, 11.5, 1.3 Hz, 1 H, H′-3), 1.65 (br t, *J* = 9.0 Hz, 1 H, H-5a), 1.55–1.31 (m, 4 H, CH_2-10, H-8a, H-6), 0.94 (t, *J* = 7.2 Hz, 3 H, CH_3-11), 0.90 (d, *J* = 7.2 Hz, 3 H, CH_3-9), 0.73 (ddd, *J* = 11.9, 11.9, 6.8 Hz, 1 H, H-8β); IR ($CHCl_3$) 3020, 1735, 1595 cm^{-1}; mass spectrum, *m/e* 218 (molecular ion); exact mass spectrum calcd for $C_{15}H_{22}O$ 218.1671, found 218.1643. (b) Data for **2b**: mp from hexane/ethyl acetate 126–127.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.8 Hz, 2 H, H-Ar), 7.36 (d, *J* = 8.8 Hz, 2 H, H-Ar), 5.98 (d, *J* = 9.8 Hz, 1 H, H-5), 5.69 (dt, *J* = 9.8, 3.3 Hz, 1 H, H-4), 3.60 (m, 1 H, H-3a), 3.44 (dd, *J* = 9.3, 1.4 Hz, 1 H, H-3), 2.64 (dd, *J* = 17.6, 8.4 Hz, 1 H, H-1β), 2.46 (s, 3 H, CH_3-Ph), 2.33 (br d, *J* = 17.6 Hz, 1 H, H-1α), 2.36–2.18 (m, 2 H, H-7, H-8b), 2.05 (dt, *J* = 12.0, 7.4 Hz, 1 H, H-8α), 1.65 (br t, *J* = 10.9 Hz, 1 H, H-5a), 1.55–1.30 (m, 3 H, H-6, CH_2-10), ca. 0.95 (m, 1 H, H-8a), 0.92 (t, *J* = 7.0 Hz, 3 H, CH_3-11), 0.87 (d, *J* = 7.2 Hz, 3 H, CH_3-9), 0.71 (ddd, *J* = 12.0, 12.0, 6.7 Hz, 1 H, H-8β); IR (CCl_4) 3024, 1748, 1592 cm^{-1}; mass spectrum, *m/e* 372 (molecular ion). Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58. Found: C, 70.78; H, 7.59.

(20) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345. Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58. Found: C, 70.78; H, 7.59.

(21) For economic and esthetic reasons, our approach focuses on the enantioselective preparation of pentenoic acid **5** via an aza-Claisen rearrangement. For preliminary results, see: Kurth, M. J.; Decker, O. H. W. *Tetrahedron Lett.* **1983**, *24*, 4535.

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On the Stability of Trimethylenemethane Dications

Summary: Substituted trimethylenemethane dications do not show the expected "Y-aromatic" stabilization in solution. The triphenyl-substituted system cyclizes to an indenyl monocation (**2**). The 2-(2-propenyl)-1,1,3-trimethylallyl cation **5** is not protonated a second time in magic acid. The highly stabilized tri(1-ethanolidene)-methane dication **9** has, however, been generated and is found to persist to at least 0 °C.

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