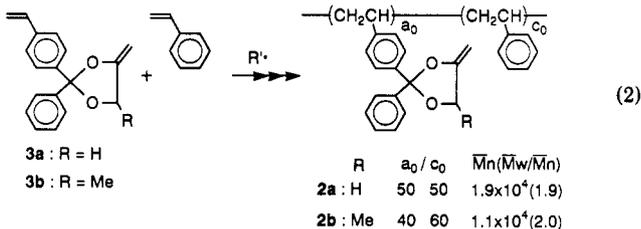


Table I. Template Polymerization of 2a and 2b

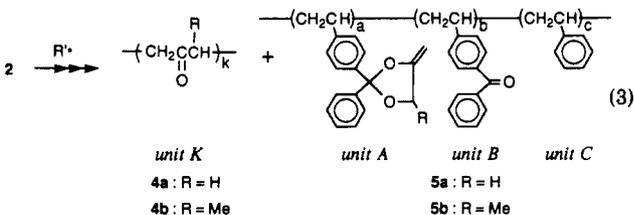
P1	T, °C	T, h	P2	composition ^b				K% ^c	IR absorption, cm ⁻¹		
				a	b	c	k		C=O	C=C	C=O
2a	120	12	4a	0	2	2	16	80	1693		
			5a	10	39	49	8		1710	1687	1659
2a	130	12	4a'	0	1	1	15	87	1693		
			5a'	2	48	49	6		1710		1659
2b	130	36	4b	0	0.5	0.8	18	93	1705		
			5b	11	29	61	<8		1670	1684	1655

^aP1 = prepolymer; P2 = postpolymer. ^bEstimated by ¹H NMR based on (a₀,c₀) = (50,50) (2a) or (a₀,c₀) = (40,60) (2b). ^cK% = k/(a + b + c + k).

The prepolymers 2a and 2b were prepared by selective radical copolymerization of styrene and the corresponding monomer 3a^{8a} or 3b^{8b} (eq 2). The polymerization of 2a was carried out at



120–130 °C in dimethylformamide (DMF) in the presence of di-*tert*-butyl peroxide (DTBP) as a radical initiator.^{9a} After 12 h, the newborn polymer 4a was collected by centrifugation from the chilled reaction mixture; 4a was insoluble in DMF at room temperature (eq 3). The obtained 4a was not cross-linked because



it could be dissolved in hot dimethylsulfoxide (DMSO). The IR spectrum of 4a showed an absorption at 1693 cm⁻¹ assigned to the C=O group of the continuous ketone unit (Figure 1B), and the ¹³C NMR spectrum showed signals at 207.06 and 35.27 ppm as carbonyl and methylene carbons of unit K, respectively. Furthermore, the ¹H NMR spectrum showed a major signal at 2.62 ppm corresponding to the methylene protons on a carbon atom adjacent to the ketone group and small signals at 7–8 ppm as aromatic protons of inseparable template polymer. From the ratio of the intensity of the signals for the methylene protons to the intensity of the signals for the aromatic protons, ketone composition (K%) of 4a on the basis of whole repeating units was estimated to be 80–87% (Table I).

The template polymer 5a was collected by precipitation in methanol from DMF solution. The IR spectra of 5a showed an absorption at 1659 cm⁻¹ assigned to a C=O group of released benzophenone side chain accompanied by a small absorption at 1710 cm⁻¹ assigned to a C=O group of isolated ketone unit, which

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(9) (a) Prepolymer 2a (1300 mg), DTBP (25.8 mg, 2 mol % based on unit A), and DMF (14.1 mL) was heated at 120 °C in a degassed sealed tube. After 12 h, the reaction mixture was chilled in a refrigerator, and white powdery 4a was collected by centrifugation. The 4a was purified by reprecipitation from cooling of hot DMSO solution and repeating centrifugation (111 mg). The supernate was poured into a methanol/triethylamine (200/1) mixture, and 5a (1141 mg) was collected as a white powder. (b) After polymerization, the reaction mixture was poured into a methanol/triethylamine mixture, and 5b was collected as a white powder by filtration. After the filtrate was concentrated by evaporation, the residue was dissolved in methylene chloride and the solution was poured into hexane. The polyketone 4b was collected by decantation as hexane-insoluble viscous liquid. All of the collected polymers were dried in vacuo over 12 h.

was incompletely separated unit K (Figure 1C). The composition of 5a was estimated by ¹H NMR and summarized in Table I. The template polymer 5a was completely recovered (yield >98%), and unit A in the 2a was decreased from 50 mol % to 2–10 mol % after polymerization, indicating that unit A was converted to unit K with releasing unit B. These results mean that radical elimination polymerization actually occurred on the side chain of prepolymer 2a, thus, 2a changed to template 5a by producing newborn polymer 4a.

The methyl-substituted prepolymer 2b was also polymerized by radical initiation at 130 °C.^{9b} The 4b was obtained from the methanol-soluble and hexane-insoluble part, whereas the template 5b was obtained from the methanol-insoluble part. The obtained 4b was built in higher ketone composition (93%) than 4a. It should be noted that the polymerization of 2b proceeds with nearly complete separation of the newborn polymer 4b and the template 5b. This phenomenon is probably attributable to retardation of the undesirable vinyl polymerization, which would lead to connection between the template and the newborn polymer by a covalent bond, prevented by the steric hindrance of the methyl group of 2b.

In conclusion, the prepolymers 2 afforded polyketones, and they themselves were converted to poly(vinylbenzophenone). Both poly(vinylbenzophenone) as template and polyketones as newborn polymer were easily separated by fractional precipitation without any particular chemical treatment after polymerization. This novel template polymerization via radical isomerization demonstrates the new concept that *polymers bear polymers*.

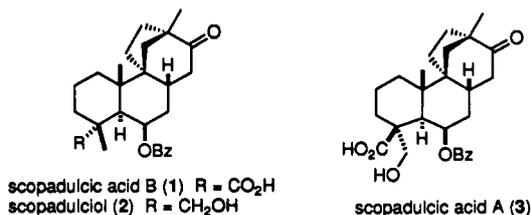
First Total Synthesis of Scopadulcic Acid B

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The medicinal plant *Scoparia dulcis* L. has long been used in Paraguay, India, and Taiwan for treating a variety of medical problems.² In recent investigations of the Paraguayan crude drug "Typychá kuratú (*Scoparidulcis* L., Scrophulariaceae), Hayashi and co-workers isolated a number of structurally unique tetracyclic diterpenes, exemplified by the scopadulcic acids B (1) and A (3) and scopadulciol (2) that are its active ingredients.³ Scopadulcic



acid B and some semisynthetic derivatives are powerful inhibitors of H⁺,K⁺-adenosine triphosphatase and as such are potential

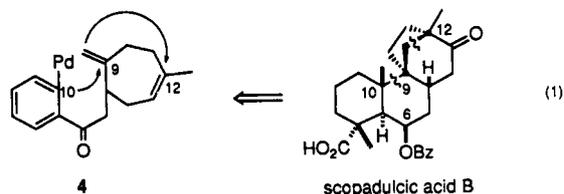
(1) (a) American Cancer Society Postdoctoral Fellow (PF-3144), 1988–1990. Current Address: Glaxo, Inc., 5 Moore Drive, Research Triangle Park, North Carolina 27709. (b) ACS Organic Division Graduate Fellow, 1990–1991.

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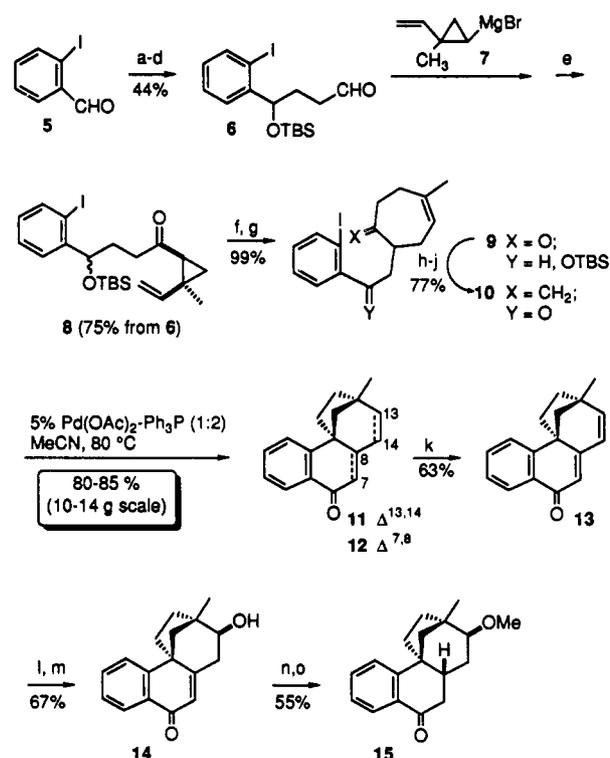
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candidates for treating peptic ulcers, gastritis, and esophagitis.⁴ Antiviral activity against herpes simplex virus type 1 and antitumor activity in several tumor cell lines also have been reported for several scopadulan diterpenes.^{5,6} We report herein the synthesis of (\pm)-scopadulic acid **1**, which constitutes the first total synthesis of a scopadulan diterpene.⁷⁻⁹ This synthetic entry, besides illustrating the power of palladium-catalyzed polyene cyclizations for forming bridged polycyclics, could enable systematic studies of the molecular basis for the diverse biological activity observed in the scopadulan series.

The significant utility of intramolecular Heck reactions for constructing congested quaternary carbon centers has only recently been appreciated.^{10,11} Our plan for accessing the scopadulic acids and congeners from a 5-methylenecycloheptene precursor is outlined schematically in eq 1. This unusual synthesis design projects construction of the scopadulan ring system and the critical quaternary centers at C(9) and C(12) of the bicyclooctane substructure in a single step.



A divinylcyclopropane rearrangement is the key step in assembling the methylenecycloheptene cyclization substrate **10** (Scheme I).¹²⁻¹⁴ The sequence begins with the 4-arylbutanal **6**, an intermediate that is readily assembled on a large scale from commercially available 2-iodobenzaldehyde. Reaction of **6** with (*Z*)-2-ethenyl-2-methylcyclopropylmagnesium bromide (**7**)¹⁵⁻¹⁷ followed by oxidation gives the cyclopropyl ketone **8**. Rearrangement of the enoxytrimethylsilane derivative of **8** in refluxing benzene followed by selective cleavage of the resulting tri-

Scheme I^a

^a Reaction conditions: (a) $\text{CH}_2=\text{CHCH}_2\text{MgBr}$, Et_2O , 0 °C, 96%; (b) TBSCl, imid., DMF, 86%; (c) $\text{BH}_3\text{-SMe}_2$, hexane, 23 °C; $\text{H}_2\text{O}_2\text{-NaOH}$ 63%; (d) Swern oxidation, 85%; (e) PCC, 3-Å molecular sieves, NaOAc, 75% from **6**; (f) TMSOTf, Et_3N , CH_2Cl_2 , 0 °C; (g) PhH, reflux; PPTS, $\text{EtOH-H}_2\text{O}$, 23 °C, 99% from **8**; (h) $\text{Ph}_3\text{P}=\text{CH}_2$, THF, 23 °C, 70-85%; (i) TBAF, THF, 23 °C, 100%; (j) PCC, 3-Å molecular sieves, NaOAc, 77% from **9**; (k) DDQ, PhCl, reflux; (l) *m*-CPBA, CH_2Cl_2 , 23 °C, 83%; (m) Te, NaBH_4 , EtOH , 80 °C, 81%; (n) LiAlH_4 , THF, -78 °C, 73%; (o) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2 , 23 °C, 75%.

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(13) All intermediates were fully characterized by ¹H and ¹³C NMR, IR, and MS analysis. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. All yields refer to isolated, purified products.

(14) The abbreviations used for standard reagents are described in *J. Org. Chem.* **1992**, *57*, 14A.

(15) Prepared in THF from the corresponding (*Z*)-bromide by sequential treatment with *t*-BuLi and $\text{MgBr}_2\cdot\text{OEt}_2$. The lithium reagent cannot be employed because it reacts with the aryl iodide functionality of **6**.

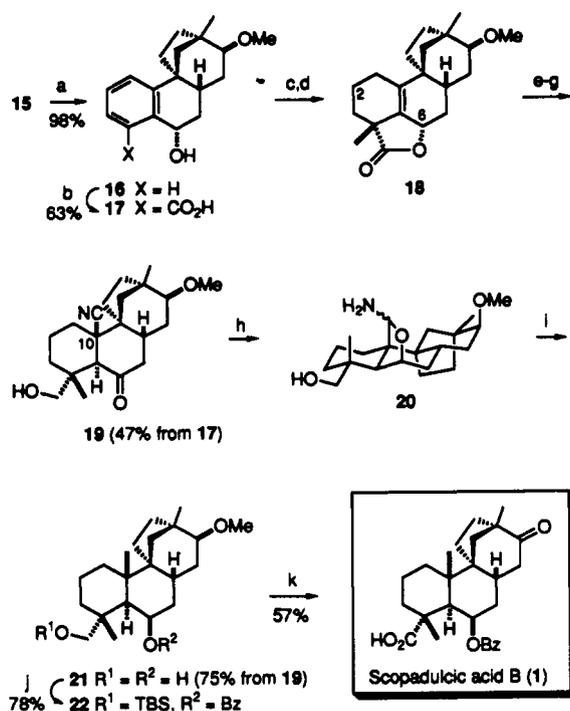
(16) The mixture of bromides formed by (*n*-Bu)₃SnH monobromination of the dibromocarbene adduct of isoprene¹⁷ can be separated on silica gel. Alternatively, the mixture of stereoisomeric bromides can be employed and the (*E*)-cyclopropyl ketone recovered after [3,3]-sigmatropic rearrangement of **8** and recycled.

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methylsilyl enol ether provided the Δ^4 cycloheptenone **9** in near quantitative yield. Transformation of this intermediate to the aryl dienone **10** was easily accomplished by standard Wittig methylation, desilylation, and oxidation. This overall sequence has been optimized to afford **10** on multigram scales in 25% overall yield from 2-iodobenzaldehyde.

The key bis-cyclization of dienyl iodide **10** was accomplished with a wide variety of palladium(0) catalysts. Preparative scale cyclizations were carried out in refluxing acetonitrile in the presence of 10 mol % of a coordinatively-unsaturated catalyst prepared from $\text{Pd}(\text{OAc})_2$ and Ph_3P . Cyclizations conducted on scales as large as 14 g provided the enones **11** and **12** in a combined yield of 80-85%. Although the amount of the rearranged enone **12** was somewhat reduced in cyclizations conducted in the presence of silver salts,^{10b} no conditions we examined completely suppressed this double bond isomerization. Face selection in the initial insertion step was not high, since the $\Delta^{13,14}$ enone **11** was formed as 1.2-1.5:1 mixture of stereoisomers.¹⁸ Although the three enone isomers could be separated, it was best to oxidize the crude cyclization product with DDQ in refluxing chlorobenzene. This treatment formed a single dienone **13** in 53% overall yield from **10**. The required oxidation at C(13) and introduction of the β -oriented methine hydrogen at C(8) were accomplished as follows. Oxidation of **13** with 1.1 equiv of *m*-chloroperoxybenzoic acid occurred cleanly at the distal double bond and from the face of the one-carbon bridge to form the β -13,14 oxide, an intermediate that could be selectively reduced¹⁹ to the hydroxy enone **14**.

(18) The major isomer has the β configuration of the C(8) methine hydrogen that is found in the scopadulic acids. This assignment was established by single crystal X-ray analysis of the epoxide prepared from the minor stereoisomer of **11**.

Scheme II^a

^a Reaction conditions: (a) LiAlH_4 , THF, -78°C ; (b) $n\text{-BuLi}$ (4 equiv), TMEDA–pentane, reflux; CO_2 , 0°C , 63% of 17 and 10% of the lactone, (c) Li , $\text{NH}_3\text{-THF}$ (4:1), reflux; isoprene; MeI; (d) H_2 , $\text{Rh}/\text{Al}_2\text{O}_3$; (e) LiAlH_4 , THF, 0°C ; (f) MnO_2 , CH_2Cl_2 , 23°C , 55% from 17; (g) Et_2AlCN , PhMe , 23°C , 85%; (h) LiAlH_4 , THF, 75°C ; (i) $\text{NH}_2\text{NH}_2\cdot 2\text{HCl}$, $\text{NH}_2\text{NH}_2\cdot \text{H}_2\text{O}$, $\text{HOCH}_2\text{CH}_2\text{OH}$, 195°C ; KOH , 195°C , 74% from 19; (j) TBSOTf , 2,6-lutidine, -70°C ; BzOTf , 2,6-lutidine, 23°C ; (k) TBAF , THF, 23°C ; $\text{RuCl}_3\cdot\text{H}_2\text{O}$, NaIO_4 , $\text{CH}_3\text{C-N-CCl}_4\text{-H}_2\text{O}$.

Reduction of this enone from the β face was best achieved by delivery of hydride intramolecularly from the C(13) alcohol.²⁰ This latter functionality was finally protected as a methyl ether to provide 15 in 37% overall yield from dienone 13 and set the stage for the critical functionalization of the aromatic ring.

Reduction of the α -tetralone 15 with LiAlH_4 at -78°C provided the equatorial alcohol 16 in near quantitative yield. Ortho lithiation of this intermediate with excess $n\text{-BuLi}$ in refluxing pentane–TMEDA²¹ followed by quenching with CO_2 afforded the benzoic acid 17 in 53% yield together with 10% of the corresponding lactone, a byproduct that was readily converted to 17, and 30% of recovered 16. Birch reduction and methylation²² proceeded to deliver, after selective saturation of the 2,3-double bond, the lactone 18 in 65% overall yield from 17.

Completion of the synthesis of scopadulcic acid B required development of the remaining quaternary center at C(10). All attempts to directly introduce this angular methyl group by conjugate addition of methyl organometallics to various intermediates having C(6) enone functionality were unsuccessful. This last obstacle was finally surmounted in an efficient, albeit classical, fashion. Sequential treatment of 18 with LiAlH_4 , MnO_2 , and Et_2AlCN ²³ provided ketone 19 in 47% overall yield from 17. The conversion of this intermediate to alcohol 21 was greatly simplified when we discovered that reduction of 19 in THF with an excess of LiAlH_4 proceeded cleanly and stereoselectively to give pentacycle 20 in essentially quantitative yield. Reduction of this re-

markably stable cyclic aminal could be accomplished in 74% yield, under forcing Wolff–Kishner conditions, to afford the tetracyclic diol 21. Silylation of the primary alcohol of 21 followed by acylation of the secondary alcohol with benzoyl triflate²⁴ provided 22, which was desilylated, and the resulting alcohol was oxidized with RuO_4 ²⁵ to afford (\pm)-scopadulcic acid B (1) in 55% overall yield from 21. Synthetic 1 showed 500-MHz ^1H NMR, 125-MHz ^{13}C NMR, and chromatographic properties that were indistinguishable from those of an authentic sample of 1.

The synthesis of scopadulcic acid B (1) summarized in Schemes I and II is capable of providing 10–100-mg amounts of 1 and congeners for pharmacological investigation. Besides being the first successful entry to this new class of biologically active terpenoids, the efficient conversion of 10 to tetracycles 11 and 12 provides the best illustration to date of the power of intramolecular Heck cyclizations to solve formidable problems in complex molecule synthesis.

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Ring Contraction of Cyclooctene, 1,3-Cyclooctadiene, 1,5-Cyclooctadiene, and Cyclooctatetraene to Benzene on Platinum(111) Surfaces

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We wish to report the discovery and mechanistic studies of the conversion of cyclic C_8 alkenes, including cyclooctene (COE), 1,3-cyclooctadiene (1,3-COD), 1,5-cyclooctadiene (1,5-COD), and cyclooctatetraene (COT), to benzene on Pt(111) surfaces under ultra-high-vacuum (UHV) conditions. This work has relevance not only for understanding important processes that occur on Pt surfaces during hydrocarbon reforming¹ but also for modeling reactions that certain organoplatinum compounds undergo during chemical vapor deposition (CVD).² Although the conversion of cyclic C_6H_6+2n hydrocarbons into benzene on a Pt(111) surface is a well-known process,^{3–5} the corresponding chemistry of cyclic

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