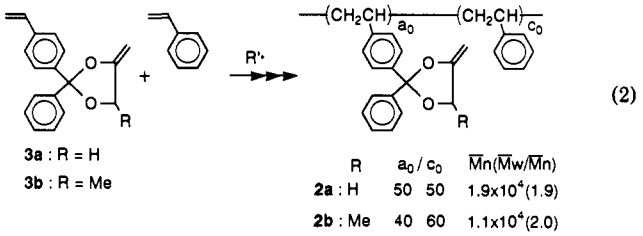
Table I. Template Polymerization of **2a** and **2b**

P1	T_1, °C	T_2, h	P2	composition[b] a	b	c	k	K%[c]	IR absorption, cm^{-1} 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 1670		
			5b	11	29	61	<8		1707	1684	1655

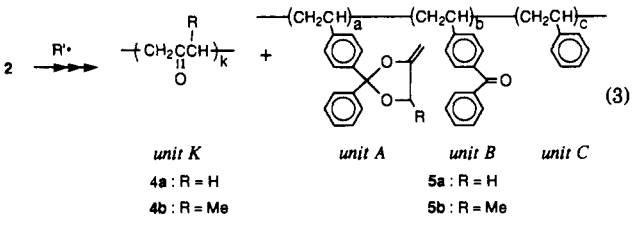
[a] P1 = prepolymer; P2 = postpolymer. [b] Estimated by ^{1}H NMR based on $(a_0,c_0) = (50,50)$ (**2a**) or $(a_0,c_0) = (40,60)$ (**2b**). [c] K% = $k/(a+b+c+k)$.

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



(2)

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



(3)

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 ^{13}C NMR spectrum showed signals at 207.06 and 35.27 ppm as carbonyl and methylene carbons of unit K, respectively. Furthermore, the ^{1}H 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 was incompletely separated unit K (Figure 1C). The composition of **5a** was estimated by ^{1}H 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*.

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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.

First Total Synthesis of Scopadulcic Acid B

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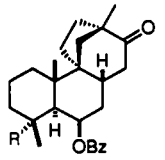
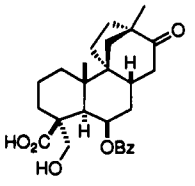
The medicinal plant *Scoparia dulcis* L. has long been used in Paraguay, India, and Taiwan for treating a variety of medical problems.[2] In recent investigations of the Paraguayan crude drug "Typychá kuratû (*Scoparicdulcis* L., Scrophulariaceae), Hayashi and co-workers isolated a number of structurally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



scopadulcic acid B (**1**) R = CO_2H
scopadulciol (**2**) R = CH_2OH



scopadulcic acid A (**3**)

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

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(2) Ganzales Torres, D. M. *Catalogo de Plantas Medicinales (y Alimenticias y Utiles) Usada en Paraguay*; Asunción: Paraguay, 1986; p 394. Chow, S. Y.; Chen, S. M.; Yang, C. M.; Hsu, H. *J. Formosan Med. Assoc.* **1974**, *73*, 729. Satyanarayana, K. *J. Indian Chem. Soc.* **1969**, *46*, 765.

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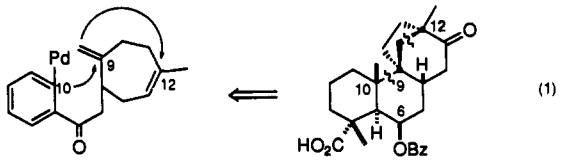
candidates for treating peptic ulcers, gastritis, and esophagitis.[4] Antiviral activity against herpes simplex virus type 1 and antitumor activity in several tumor cell lines also have been reported for several scopadulan diterpenes.[5,6] We report herein the synthesis of (±)-scopadulcic acid B (**1**), 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, should enable systematic studies of the molecular basis for the diverse biological activity observed in the scopadulan series.

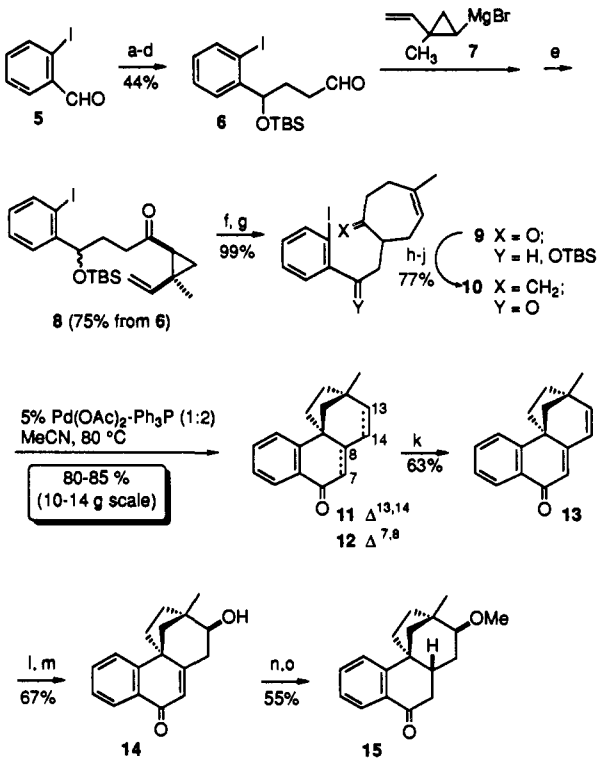
The significant utility of intramolecular Heck reactions for constructing congested quaternary carbon centers has only recently been appreciated.[10,11] Our plan for accessing the scopadulcic acids and congeners from a 5-methylenecycloheptene precursor is outlined schematically in eq 1. This unusual 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.



4 scopadulcic acid B (1)

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 trimethylsilyl 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 methylenation, desilylation, and oxidation. This overall sequence has been optimized to afford **10** on multigram scales in 25% overall yield from 2-iodobenzaldehyde.

Scheme I[a]



[a] Reaction conditions: (a) CH_2=$CHCH_2MgBr$, Et_2O, 0 °C, 96%; (b) TBSCl, imid., DMF, 86%; (c) BH_3·SMe_2, hexane, 23 °C; H_2O_2–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, EtOH–H_2O, 23 °C, 99% from **8**; (h) Ph_3P=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%.

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 $Pd(OAc)_2$ 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 reduced[19] to the hydroxy enone **14**.

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(13) All intermediates were fully characterized by ^1H and ^{13}C 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 $MgBr_2$·OEt_2. The lithium reagent reagent cannot be employed because it reacts with the aryliodide functionality of **6**.

(16) The mixture of bromides formed by (*n*-Bu)$_3$SnH monodebromination of the dibromocarbene adduct of isoprene[17] 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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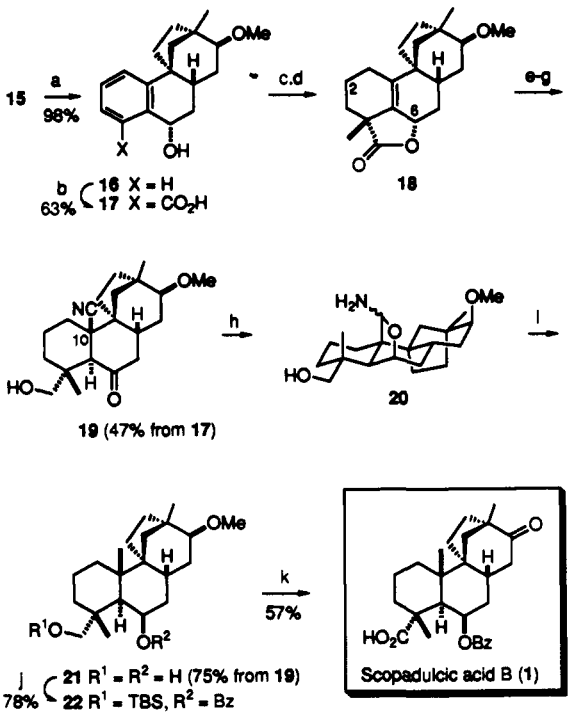
(18) The major isomer has the β configuration of the C(8) methine hydrogen that is found in the scopadulcic acids. This assignment was established by single crystal X-ray analysis of the epoxide prepared from the minor stereoisomer of **11**.

Scheme II[a]



[a] Reaction conditions: (a) $LiAlH_4$, THF, -78 °C; (b) *n*-BuLi (4 equiv), TMEDA-pentane, reflux; CO_2, 0 °C, 63% of **17** and 10% of the lactone, (c) Li, NH_3-THF (4:1), reflux; isoprene; MeI; (d) H_2, Rh/Al_2O_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) $NH_2NH_2 \cdot 2HCl$, $NH_2NH_2 \cdot H_2O$, $HOCH_2CH_2OH$, 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; $RuCl_3 \cdot H_2O$, $NaIO_4$, CH_3CN-CCl_4-H_2O.

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*-BuLi in refluxing pentane-TMEDA[21] 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 methylation[22] 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 remarkably 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 triflate[24] provided **22**, which was desilylated, and the resulting alcohol was oxidized with RuO_4[25] to afford (±)-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 reforming[1] 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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