Total Synthesis of (±)-Scopadulcic Acid A. An Illustration of the Utility of Palladium-Catalyzed Polyene Cyclizations

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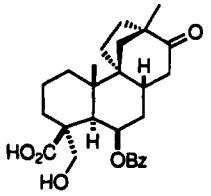
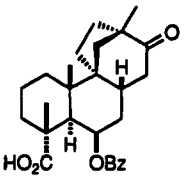
Summary: The first total synthesis of (±)-scopadulcic acid A has been accomplished using an intramolecular bis-Heck cyclization to form the B–D rings of this tetracyclic diterpene with complete stereocontrol.

The plant *Scoparia dulcis* has long been used in the traditional practice of medicine in Paraguay, India, and Taiwan.[2] In a search for biologically active substances from the Paraguayan crude drug "Typychá kuratû", Hayashi and co-workers described in 1987 the isolation from *Scoparia dulcis* L. (Scrophulariaceae) of two structurally novel tetracyclic diterpene acids, the scopadulcic acids A (1) and B (2).[3] Preliminary investigations reveal a remarkable pharmacological spectrum for the scopadulan diterpenes: in vitro and in vivo antiviral and antitumor activities and powerful inhibitory activity against H^+,K^+-adenosine triphosphatase (the proton pump for gastric acid secretion).[3c,4] We recently reported the total synthesis of (±)-scopadulcic acid B, which was the first total synthesis of a scopadulan diterpene.[5] Herein we record the first total synthesis of scopadulcic acid A by a strategy that is more direct than our first generation entry to this unusual class of pharmacological agents.



scopadulcic acid A (1)



scopadulcic acid B (2)

A bis-Heck cyclization of a methylenecycloheptenyl aryl ketone was the central step in our synthesis of scopadulcic acid B (Figure 1, 3 → 2).[5,6] Since an aromatic ring is not an ideal structural template for evolving the two quaternary centers of the scopadulan A ring, our second generation approach adopted a seco-A ring strategy in which bis-cyclization of a monocyclic trienyl iodide would be the central step (Figure 1, 4 → 1 or 2). An additional key objective of this second generation strategy was to control face selection in the initial insertion of the exomethylene group by incorporating a β-alkoxy substituent at C(6) in the cyclization substrate 4. The rationale for this choice is depicted in Figure 1, where a preferred eclipsed orientation[7] of the C–Pd σ-bond and the exomethylene group places the alkoxy substituent in an unhindered equatorial environment.

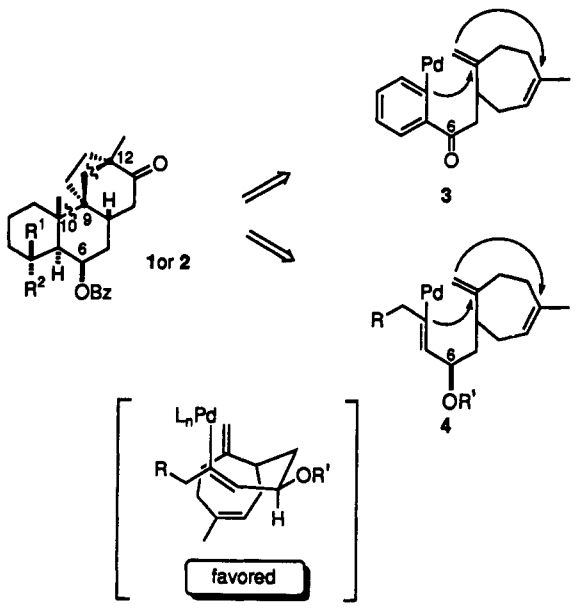


Figure 1. Synthesis plan.

Methylenecycloheptene aldehyde 9, the precursor of the cyclization substrate 12, was assembled using a divinylcyclopropane rearrangement strategy similar to that employed in our earlier synthesis of scopadulcic acid B.[5,8] One change merits note. We found it considerably more convenient not to resolve the stereoisomers of cyclopropyl bromide 5, but rather to use the readily available isomer mixture[9] to prepare the cyclopropyl ketones 6. Thermal

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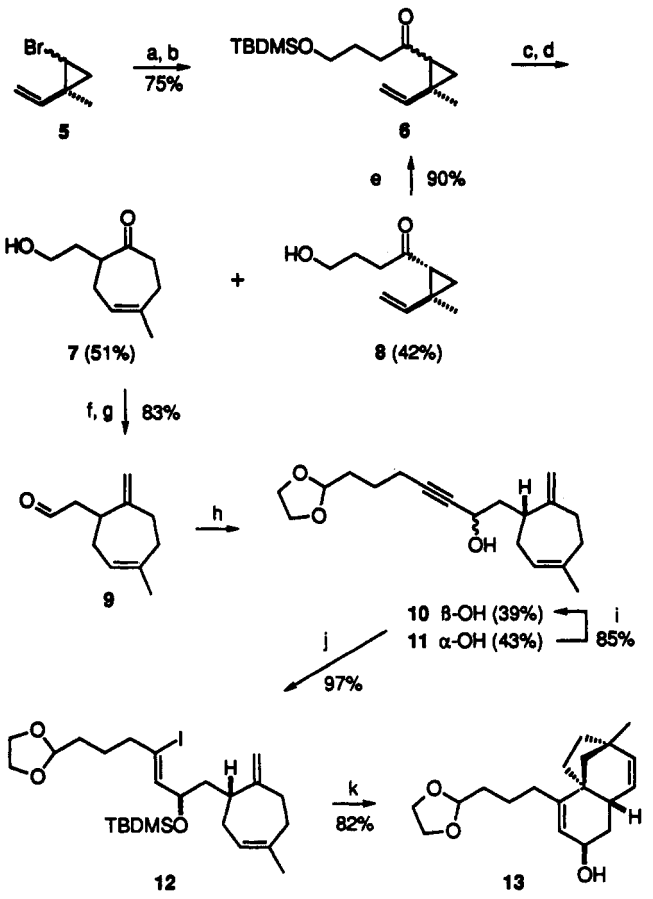
Scheme I[a]

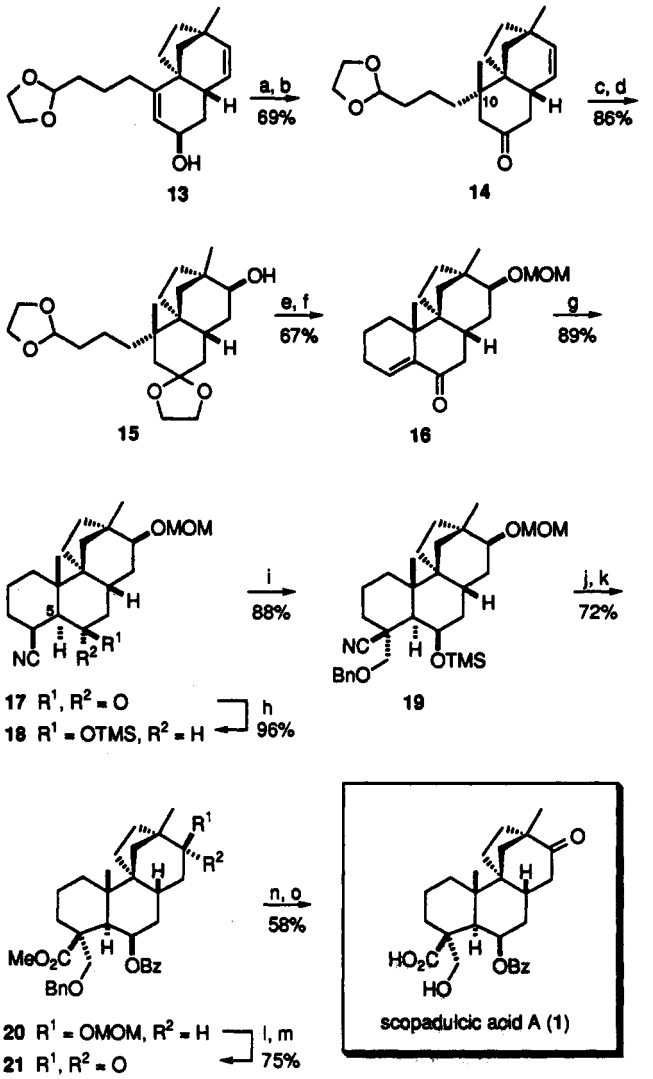


[a] Reaction conditions: (a) *t*-BuLi, Et_2O, −78 °C; $TBDMSO(CH_2)_3CHO$, −78 → 23 °C; (b) Swern oxidation; (c) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; (d) PhH, reflux; PPTS, *i*-PrOH–H_2O, 23 °C; TBAF, THF, 23 °C; (e) NaOMe, MeOH, reflux (*Z*:*E* = 3:4); TBSCl, imidazole; (f) $Ph_3P{=}CH_2$, DMSO, 23 °C, 91%; (g) Swern oxidation, 91%; (h) $(OCH_2CH_2O)CH(CH_2)_3C{\equiv}CLi$, THF, −78 → 23 °C; separation on silica gel; (i) Ph_3P, DEAD, $PhCO_2H$, −20 → 23 °C; K_2CO_3, MeOH; (j) Red-Al, THF, 23 °C; NIS, −70 → 23 °C; TBDMSCl, imidazole, DMF; (k) 10% $Pd(OAc)_2$–Ph_3P (1:2), Ag_2CO_3, THF, reflux; TBAF, THF, 23 °C.

rearrangement of the enoxysilanes derived from these intermediates afforded, after desilylation, a readily separable mixture of cycloheptenone **7** and the *trans*-cyclopropyl ketone **8**.[10] Recycling this latter intermediate allowed **9** to be prepared in 75% overall yield from the ~1:1 mixture of cyclopropyl ketones **6**.

Reaction of aldehyde **9** with [6-(ethylenedioxy)-1-hexynyl]lithium[11] provided a ~1:1 mixture of propargylic alcohols **10** and **11**, which could be separated by careful chromatography on silica gel. Mitsunobu inversion[12] of the undesired α-epimer **11** allowed **10** to be prepared in 78% yield from **9**. Reduction of **10** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al),[13] iodination of the resulting vinylalanate, and protection of the allylic alcohol gave the *Z* trienyl iodide cyclization substrate **12**. The critical bis-Heck cyclization of **12** proceeded cleanly in refluxing THF in the presence of 10% $Pd(OAc)_2$, 20% Ph_3P, and 2 equiv of Ag_2CO_3 to give, after desilylation, a *single* tricyclic product **13** in 82% yield. That the initial insertion occurred with complete stereochemical fidelity in the desired sense was established in a related series (OTBDMS instead of ethylene acetal) by X-ray analysis.[14] The efficient sequence summarized in Scheme I provided **13** on multigram scales in 31% overall yield from the mixture of cyclopropyl bromides **5** (16% overall from isoprene).

Scheme II[a]



[a] Reaction conditions: (a) TPAP, NMO, CH_2Cl_2–CH_3CN, 23 °C, 88%; (b) Me_2Zn, LiBr, $Ni(acac)_2$, Et_2O, 23 °C; 78%; (c) $(CH_2OH)_2$, $(OCH_2CH_2O)CHOMe$ Amberlyst 15, Me_3CN; 23 °C, 91%; (d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C; $LiAlH_4$, THF, 23 °C, 94%; (e) 20% aqueous HCl–MeOH, 65 °C, 87%; (f) MOMCl, $(i\text{-}Pr_2)NEt$, CH_2Cl_2, 77%; (g) Et_2AlCN, THF, 0 °C; TMSCl, Et_3N, 0 °C; dilute aqueous HCl, 23 °C; (h) $LiAlH_4$, THF, −78 °C, 99%; TMSCl, DMAP, pyridine–CH_2Cl_2, 0 °C, 97%; (i) LDA, THF, 0 °C; $BnOCH_2Br$, −78 → 0 °C; (j) KOH, K_2CO_3, 140 °C; CH_2N_2, Et_2O, 0 → 23 °C, 82%; (k) BzCl, DMAP, pyridine, 100 °C; (l) HCl, MeOH, 70 °C, 82%; (m) PCC, 4-Å molecular sieves; CH_2Cl_2, 23 °C, 91%; (n) *n*-PrSLi, DMPU, 23 °C, 60%; (o) H_2, Pd–C, EtOAc–MeOH, 23 °C, ~100%.

The efficient elaboration of **13** to the scopadulan ring system is summarized in Scheme II. The critical angular methyl group at C(10) was introduced by oxidation of **13** to form the corresponding enone[15] followed by reaction of

(10) 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 combustional analysis or high-resolution mass spectrometry. Yields refer to isolated, purified products unless noted otherwise.

(11) Prepared from 5-hexynol by oxidation (ClCOCOCl, Me_2SO, Et_3N) followed by acetalization ($HOCH_2CH_2OH$, *p*-TsOH).

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this intermediate with Me_2Zn/Ni(acac).[16] Conjugate addition of methyl occurred with complete facial selectivity from the same face as the one-carbon bridge to give **14** in 69% overall yield from **13**.[17] The oxygen functionality of the C ring was next developed by protection of the C(6) ketone of **14**, epoxidation of the resulting bis-ketal, and regioselective reduction of the derived β-epoxide to provide **15**. Treatment of this intermediate with dilute methanolic HCl afforded the crystalline (mp 115–117 °C) tetracyclic enone in one step. Standard protection of the hydroxy group then provided the MOM ether **16** in 67% yield. Enone **16** is a potentially versatile intermediate for preparing a variety of scopadulan diterpenes and analogs and is available on preparative scales in 15 total steps and 5% overall yield from **5**.

(±)-Scopadulcic acid A was prepared from the tetracyclic enone **16** as follows. Reaction of **16** with Et_2AlCN and Me_3SiCl, followed by hydrolysis with dilute HCl, provided **17** (mp 171–172 °C) in 89% yield.[18] Reduction of **17** with $LiAlH_4$ at −78 °C provided exclusively the axial C(6) alcohol, which was silylated to provide **18**. The remaining carbon appendage at C(4) was then introduced, with complete stereocontrol, by reaction of the lithium salt of nitrile **18** with (benzyloxy)methyl bromide to afford **19** in 84% yield from **17**. Although the hindered axial nitrile group of **19** was stable to many common hydrolysis conditions, it could be transformed to the carboxylate salt by heating a mixture of **19**, KOH, and K_2CO_3 at 140 °C. Careful acidification, esterification of the resulting acid, and benzoylation of the liberated C(6) alcohol group with BzCl and DMAP at 100 °C in pyridine provided **20** in 72% overall yield. Using conventional transformations, tetracycle **20** was finally converted to the natural diterpene acid by transformation of the MOM ether to a carbonyl group, followed by sequential deprotection of the carboxylic acid and alcohol functionalities of **21**. Although these final stages are yet to be fully optimized, (±)-scopadulcic acid A (**1**), mp 237–239 °C dec, was available from **20** in ~45% overall yield. Synthetic **1** showed 500 MHz ^1H NMR, 125 MHz ^{13}C NMR, and chromatographic properties that were indistiguishable from those of an authentic sample of **1**.

This more direct total synthesis route to the scopadulan diterpenes successfully addresses several of the shortcomings of our first generation approach. Most notable is the complete stereocontrol now realized in the critical bis-Heck cyclization and the more direct elaboration from an acyclic precursor of the two quaternary centers of the scopadulan A ring. These improvements will facilitate the synthesis of congengers of **1** and **2** for future pharmacological investigation.

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Supplementary Material Available: Characterization data for new compounds and ^1H and ^{13}C NMR spectra of natural and synthetic scopadulcic acid A (9 pages). This material is contained in 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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