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(−)-Isoscopariusin A, a Naturally Occurring Immunosuppressive Meroditerpenoid: Structure Elucidation and Scalable Chemical Synthesis

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Abstract: *(−)-Isoscopariusin A was isolated from the aerial parts of Isodon scoparius. Chemical synthesis and spectroscopic analysis established its structure as an unsymmetrical meroditerpenoid bearing a sterically congested 6/6/4 tricyclic carbon skeleton with seven continuous stereocenters. A gram-scale synthesis was achieved in 12 steps from commercially available (+)-sclareolide. A cobalt catalyzed, hydrogen atom transfer-based olefin isomerization was used to prepare a trisubstituted alkene, which underwent stereoselective [2+2] cycloaddition with a substituted keteniminium ion generated in situ from the corresponding amide. The cyclobutanone product was further elaborated into the fully substituted cyclobutane core through face-selective homologation, and the two side chains were installed by using nickel-catalyzed cross-electrophile coupling and carbodiimide-mediated esterification, respectively. (−)-Isoscopariusin A displayed selective inhibition of T-cell proliferation.*

Introduction

Immunosuppressive agents are used for protecting transplanted organs from a host's immune system response as well as treating autoimmune and inflammatory diseases.[1] A number of immunosuppressive drugs have been used clinically, such as cyclosporine A, FK506, and rapamycin.[2] However, their side effects including hepatoxicity and nephrotoxicity turn out to be a severe problem.[3] Natural products have proven to be a rich source of immunosuppressive agents.[4] Therefore, searching for naturally occurring novel immunosuppressants is of remarkable medical interest. Since the discovery of the fungal metabolite, cyclosporine A, in 1970, a series of natural products derived from microbes have been reported to possess considerable immunosuppressive activity.[4c,5] Moreover, natural immunosuppressive agents derived from plants have aroused increasing attentions of chemists.[6]

Isodon species have attracted considerable interest among organic chemists because they are rich in structurally and biologically interesting diterpenoids.[7] *Isodon scoparius*, a rare herbage, has been used as an antipyretic agent by local inhabitants in Shangrila City of Yunnan Province, P. R. China. Our previous search for bioactive constituents from this species has led to the discovery of three structurally unusual meroditerpenoids, scopariusic acid[8] and scopariusicides A and B.[9] These compounds feature a densely substituted cyclobutane ring and exhibit immunosuppressive activities. Notably, we accomplished the synthesis of scopariusicide A by exploiting an amide directed C–H arylation (Pd-catalyzed sp^3 C–H bond β-arylation). Our continuing exploration for the low-abundance constituents of *I. scoparius* resulted in the discovery of (−)-isoscopariusin A (**1**, Figure 1), a novel meroditerpenoid with an unprecedented 6/6/4 tricyclic carbon skeleton bearing a fully substituted cyclobutane ring and seven contiguous stereocenters. However, the confirmation of the stereochemistry of **1**, in particular, the congested cyclobutane core and the C3″ stereocenter at the side chain, proved to be a problem. Due to the low-abundance from natural source and ambiguous structure, a chemical synthesis of **1** could not only confirm all the stereocenters indubitably but also enable further biological study.[10]

Due to the fascinating architectures as well as remarkable biological activities of the cyclobutane-containing natural products, an increasing number of novel approaches targeting these unique structures have emerged.[11] The assembly of an unsymmetrical cyclobutane ring in a controlled and efficient fashion in these unique structures has long been highly desirable. [2+2] cycloadditions provide a direct and atom-economical approach to access the cyclobutane scaffold with up to four stereocenters in a single step.[12] While different

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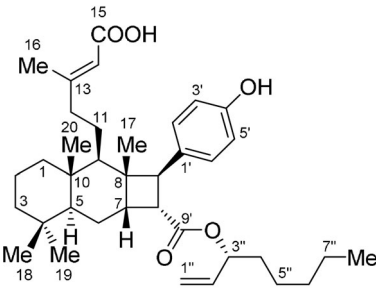


1: (–)-isoscopariusin A

Figure 1. Structure of (−)-isoscopariusin A (**1**).

kinds of reactions including [2+2] photocycloaddition, oxidative radical and acid-catalyzed [2+2] cycloaddition have rendered a handful of cyclobutane-containing structures, it remains uncertain whether or not the existing synthetic methods and strategies can be used to access efficient synthesis for the unprecedented cyclobutane-containing meroditerpenoid **1**. Herein, we report the structure elucidation and scalable chemical synthesis of (−)-isoscopariusin A (**1**) and its significant immunosuppressive selectivity on T lymphocytes. A gram-scale synthesis of **1** was achieved in 12 steps from commercially available (+)-sclareolide.

Results and Discussion

Structure Elucidation and Plausible Biogenetic Pathway of 1

(−)-Isoscopariusin A (**1**) was obtained as colorless gum, with the molecular formula $C_{37}H_{54}O_5$, as established by a (+)-HREIMS ion peak at *m/z* 578.3941 $[M]^+$ (calcd 578.3971) and eleven double bond equivalents (DBEs). The ^{1}H NMR spectrum displayed signals due to one 4-substituted phenyl, one terminal olefin and one trisubstituted olefin, one oxygenated methine, four tertiary methyls, one secondary methyl and one olefinic methyl (Table S1 in the Supporting Information). Analysis of the ^{13}C NMR and HSQC spectra revealed 37 carbon signals assigned to six methyls, eleven methylenes (containing one sp^2 methylene), twelve methines (containing six sp^2 methines and one oxygenated), and eight quaternary carbons (including two carbonyls and three sp^2 carbons).

Comprehensive analysis of 2D NMR spectra allowed the establishment of the planar structure of **1** as a meroditerpenoid. Interestingly, the NMR data for **1** indicated that it can be subdivided into three distinct structural fragments (Figure 2): a labdane-type diterpene nucleus (part A), a phenylpropanoid derivative (part B), and a C8 fatty alcohol (part C). Part A was found to be similar to the diterpene nucleus of labda-7,13*E*-dien-15-oic acid,[13] except that the C7-C8 double bond was saturated in **1**, which was proven by the HMBC correlations from H-7 to C-5, C-8, C-9 and C-17. Part B was deduced by the ^{1}H-^{1}H COSY correlations of H-7′/H-8′, H-2′/H-3′, and H-5′/H-6′, together with the HMBC correlations from H-2′, H-6′ to C-4′, C-7′, H-3′, H-5′ to C-1′, C-4′, H-7′ to C-9′, and H-8′ to C-1′, C-9′. Part C was identified as 1-octene-3-ol on the basis of ^{1}H-^{1}H COSY correlations (H_2-1″/H-2″/H-3″/H_2-4″/H_2-5″/H_2-6″/H_2-7″/H_3-8″), together with the HMBC correlations from H-1″ to C-3″, H-3″ to C-5″, H-4″ to C-2″, H″-7 to C-5″, and H-8″ to C-6″. Parts A and B were directly linked to form a four-membered ring via C-7/C-8/C-7′/C-8′ based on the ^{1}H-^{1}H COSY correlations (H_2-6/H-7/H-8′/H-7′), along with HMBC correlations from H_3-17 to C-9, C-7′, H-7 to C-9′, and H-8′ to C-8. In addition, Parts B and C were connected via a C–O bond on the basis of the key HMBC correlation from H-3″ to C-9′.

The relative configuration of **1** was partially assigned by a ROESY spectrum (Figure 2). The ROESY correlations for H-2′, H-6′ with H-7, H-8′, H_3-17, and H-7/H_3-17, H_3-17/H_3-20, H-7/H-8′ indicated that H-7, H-8′ and Me-17 were cofacial, which were arbitrarily assigned to be β-orientated. The ROESY correlation of H-7′ with H-9 suggested that H-7′ adopted an α-orientation. However, the determination of the relative configuration at C-3″ was challenging due to its location at the freely rotating side chain.

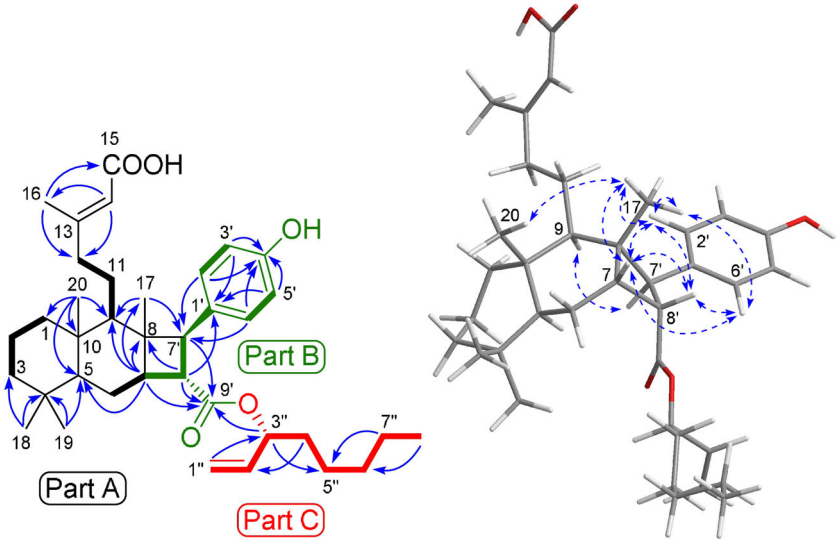
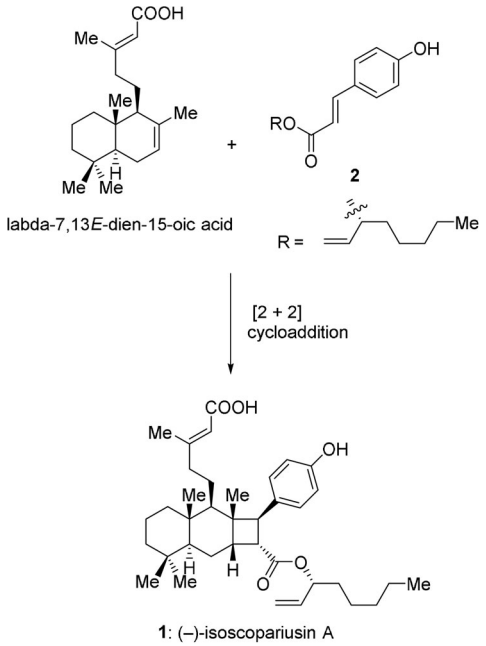


Figure 2. Key ^{1}H-^{1}H COSY (bold), HMBC correlations (blue arrows) and ROESY correlations (dashed arrows) of **1**.

Biogenetically, **1** might be formed via enzyme-dependent intermolecular [2+2] cycloaddition between a labdane diterpenoid (labda-7,13*E*-dien-15-oic acid) and an unusual ester **2** of 4-hydroxycinnamic acid and (*R*)-1-octene-3-ol (Scheme 1). Therefore, based on comparisons with reported NMR data for analogues[8,9] and a plausible biogenetic pathway, the orientation of H-3″ was arbitrarily deduced to be β-orientated. However, we cannot confirm the absolute configuration due to the sterically congested four-membered ring and the C8 side chain, and attempts to obtain single crystals suitable for X-ray diffraction experiments failed. Aiming to provide unambiguous confirmation of the stereochemistry for the naturally scarce meroditerpenoid **1** and further explore its bioactivity, we engaged to develop an efficient strategy for the synthesis of **1**.



Scheme 1. Hypothetical biogenetic pathway of **1**.

Attempts to Construct the 6/6/4 Tricyclic Core of 1 Based on a Photochemical [2+2] Cycloaddition Approach

Our first instinct was to apply intermolecular photochemical [2+2] cycloaddition to biogenetically construct the 6/6/4 tricyclic carbon skeleton (Figure 3). The stereoselective functionalization of poly-substituted cyclobutane derivatives is a key issue for the synthesis. Photochemical [2+2] cycloaddition reactions involving compounds with an unsaturated carbonyl, cycloalkenyl esters and olefins have proved to be one of the most useful stereoselective approaches to assemble cyclobutane derivatives.[14] Thus, we envisaged an intermolecular photochemical [2+2] cycloaddition reaction for the consecutive C7, C8, C7′ and C8′ stereocenters. In this strategy, **1** is expected to be constructed through photochemical [2+2] cycloaddition between phenylpropanoid derivatives of **2** and trisubstituted alkene **3**, which can be tracked back to the (+)-sclareolide (**4**) from commercial sources. The alkene **7**

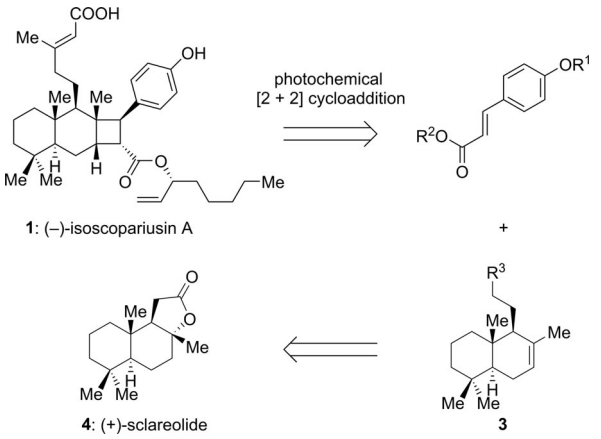
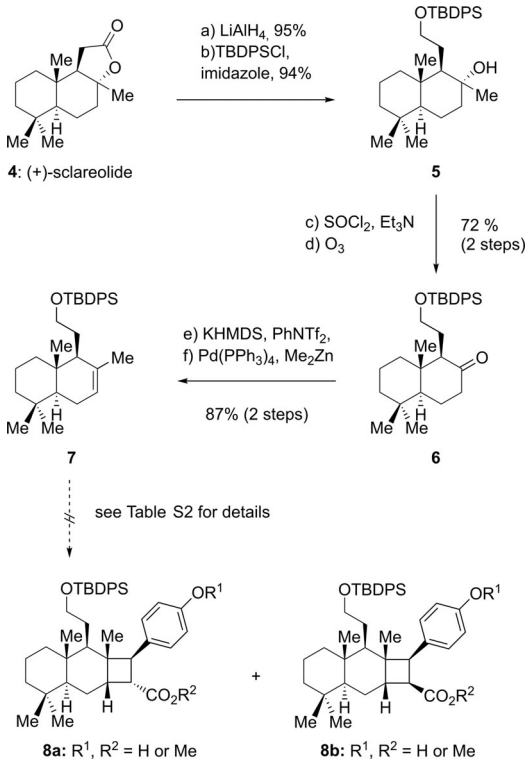


Figure 3. Retrosynthetic analysis of **1** based on a photochemical [2+2] cycloaddition approach.

was smoothly prepared on the gram scale from the available **4** via a developed protocol (regioselective elimination of **5** to terminal alkenes,[15] ozonolysis, regioselective formation of vinyl triflate and Negishi coupling reactions) (Scheme 2).

With an ample amount of **7** in hand, we examined different conditions for photochemical [2+2] cycloaddition reactions (Table S2 in the Supporting Information). Direct intermolecular [2+2] photocycloaddition was conducted with diverse modified forms of **2** and additives (including acetophenone and benzophenone). As a result, no desired product was observed, and a mixture of cis and trans cinnamic acid derivatives was isolated. It suggested that the intermolecular



Scheme 2. Attempts to construct the 6/6/4 tricyclic core of **1** based on a [2+2] photocycloaddition approach.

[2+2] photocycloaddition may be hindered for the large aromatic substitute, and that the *Z*/*E* isomerization of the acyclic double bond in the precursors can occur. The visible photoredox conditions developed by Yoon[16] was also tested, but it proved to be fruitless in this particular case.

First Route for the Synthesis of the Tricyclic Core of 1 through Ketene-Based [2+2] Cycloaddition

Classical [2+2] cycloadditions of dichloroketene to olefins can provide a dichlorocyclobutone adduct with highly regio- and stereoselectivity.[17] We envisaged that the key intermediate **9** can be derived from [2+2] cycloaddition of trisubstituted alkene **3** with dichloroketene **10**, which can be in situ generated from **11** (Figure 4).

To our delight, the alkene **7** underwent a smooth highly regio- and stereoselective cycloaddition in the presence of trichloroacetyl chloride and active zinc to deliver the adduct **12** (Scheme 3). SmI_2-mediated reduction efficiently provided cyclobutanone **13**. A mixture of **14** and its regioisomer (1:1.3) was obtained in 61% yield involving vinyl triflate (KHMDS, $PhNTf_2$, −78°C) and subsequent carbonylative coupling [$Pd(Ph_3P)_4$, CO, 22°C].[18] Compound **14** was obtained as a single regioisomer by treatment of **13** with 2,4,6-triisopropylbenzenesulfonyl hydrazide (Tris-$NHNH_2$) and Na_2SO_4 as a dehydrating reagent, followed by Shapiro coupling reaction with careful handling with Tris-hydrazone (e.g., rather labile, hygroscopic and irreproducible reaction results).[19] Arylation of **14** with Grignard reagent **15** and CuBr•SMe_2 afforded a single product **16**. Detailed analysis of its NMR spectrum indicated that the H-7′ and H-8′ configurations were cofacial. To obtain its stereoisomer **18**, **16** was first treated with a base, but it resulted in no conversion under thermodynamic (DBU, toluene, 80°C) and kinetic (LDA, THF, −78°C) conditions, respectively. To our delight, we managed to obtain the desired adduct **18** in a two-steps approach[20] (KHMDS, PhSSPh; H_2/Raney Nickel) in 23% yield, along with its C8′ epimer **16** (51%) that can be recycled. Deprotection of **18** followed by bromination furnished the bromide **19**. The stereochemistry of the thiophenyl derivative **17a** and the bromide **19** was corroborated by X-ray crystallographic analysis (Figure 5). Following the "from south to north" strategy, we managed to install the adjacent C7′ and C8′ stereocenters via Shapiro coupling reaction, 1,4-addition and configuration inversion.

To improve the efficiency of the synthesis, we directed our attention to the first α-arylation of cyclobutanone **13** followed by installation of the chiral C′8 stereocenter (Scheme 4). Attempts to proceed the Ni-catalyzed arylation of the α-chloroketone **20** met with failure.[21] Under the conditions reported by Britton and co-workers for the arylation of cyclobutanones [(D′BPF)$PdCl_2$, LiO^tBu, 4-bromoanisole, THF, 60°C],[22] α-arylcyclobutanone **21** was obtained from cyclobutanone **13** in 23% yield due to the poor diastereoselectivity.

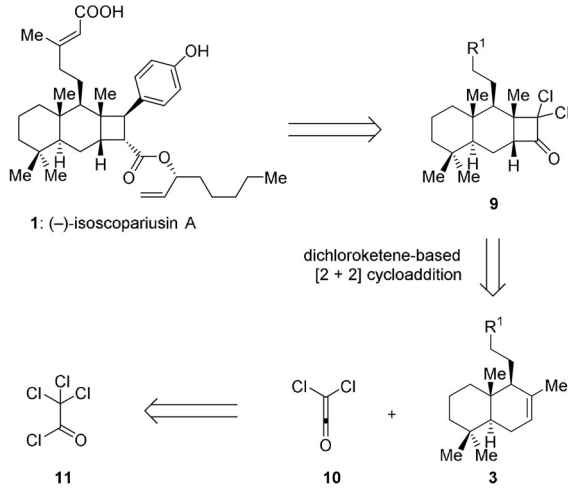
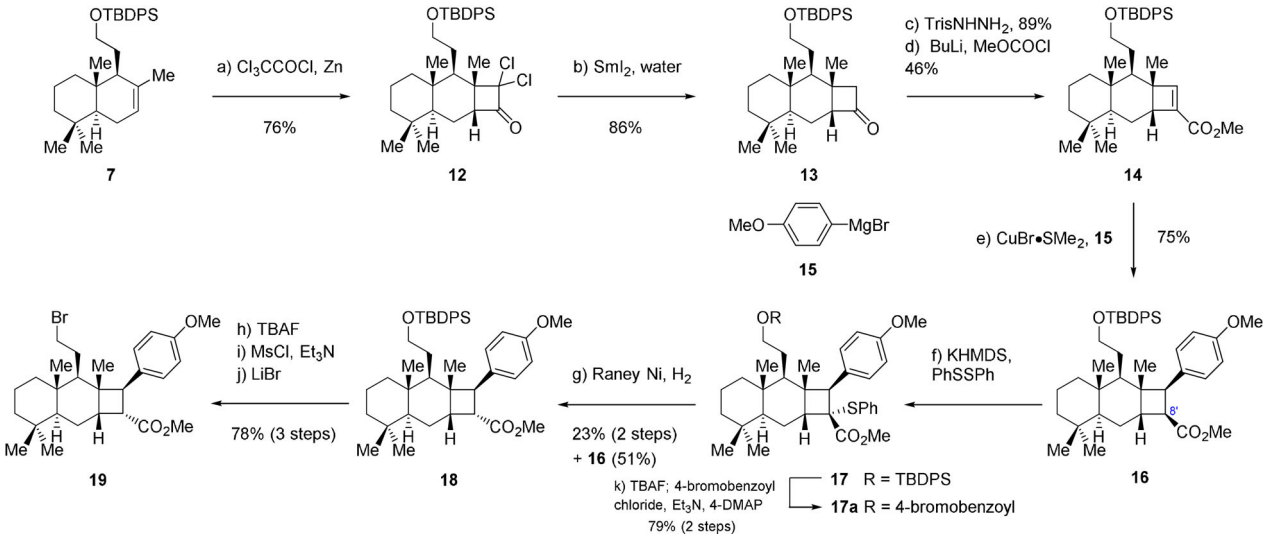


Figure 4. Retrosynthetic analysis of **1** through dichloroketene-based [2+2] cycloaddition.



Scheme 3. First route for the synthesis of the tricyclic core of **1**.

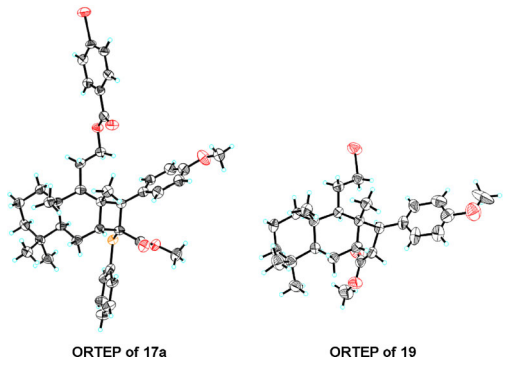
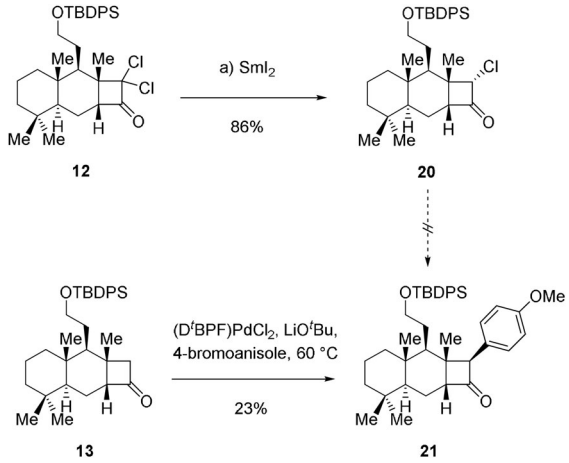


Figure 5. ORTEP drawings of compounds **17a** and **19**.[34]



Scheme 4. Attempts to access α-arylcyclobutanone **21** via cross-coupling reaction.

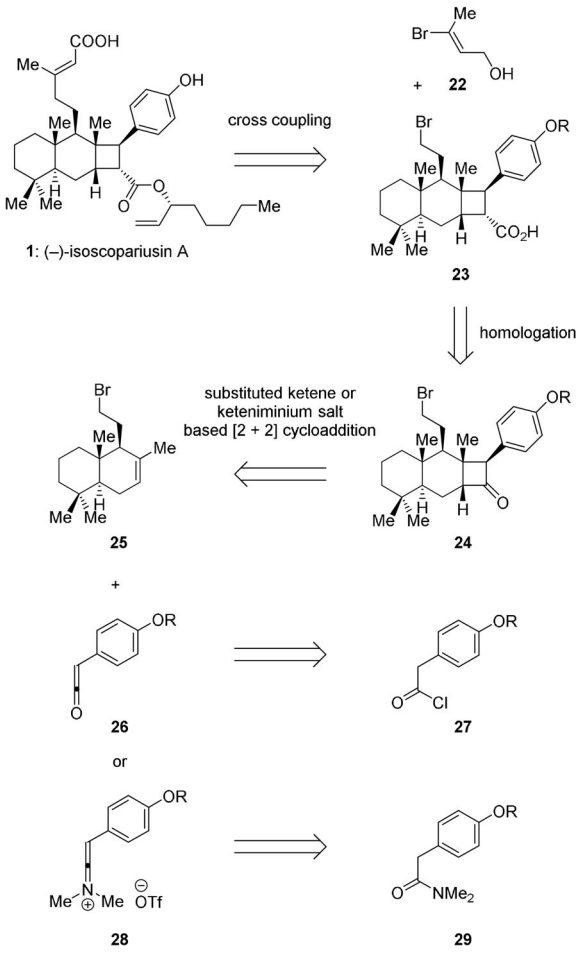
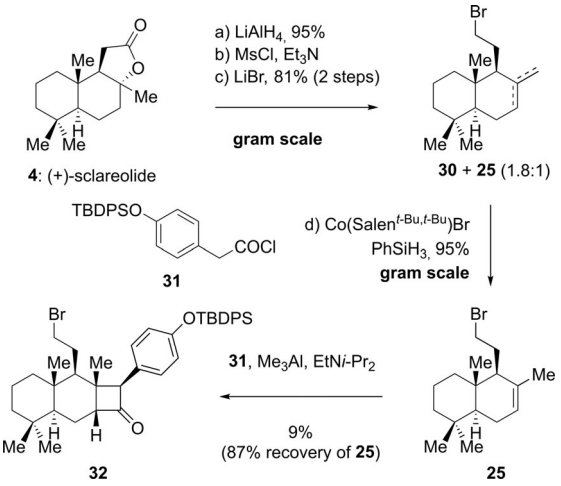


Figure 6. Retrosynthetic analysis of **1** through substituted ketene or keteniminium salt based [2+2] cycloaddition.

Construction of α-Arylcyclobutanone 32 through Substituted Ketene or Keteniminium Salt Based [2+2] Cycloaddition

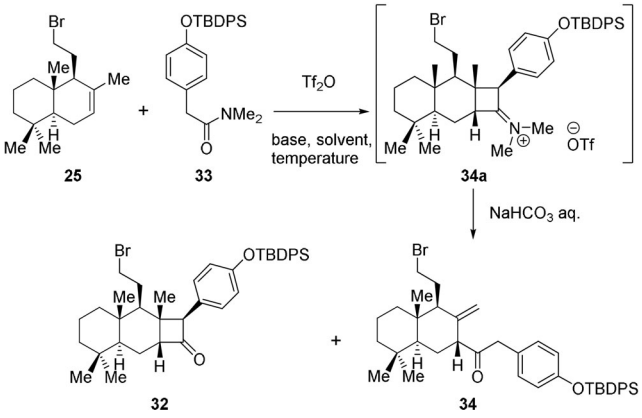
In the first route for the synthesis of the tricyclic core of **1**, **19** from **7** (Scheme 3), intermolecular [2+2] thermal cycloaddition between dichloroketene and trisubstituted alkene was applied to assemble dichlorocyclobutanones. Although Shapiro coupling reaction followed by 1,4-addition furnished the key intermediate with a functionalized cyclobutane core bearing two chiral centers, the mismatched C8′ stereochemistry and the subsequent operation of configuration inversion significantly lowered the overall efficiency. Therefore, we explored an alternative strategy in which α-arylcyclobutanones were first established, followed by face-selective homologation to access the key cyclobutane skeleton with four chiral centers. With these thoughts in mind, we undertook a retrosynthetic analysis of **1** (Figure 6). Disassembly of the meroditerpenoid afforded the cross-coupling precursors **22** and **23**. Acid **23** can be traced back to α-arylcyclobutanone **24** via stereo-controlled homologation. We envisaged that α-arylcyclobutanone **24** could be rendered via substituted ketene or keteniminium salt-based [2+2] cycloaddition of alkene **25** in a "from North to South" strategy instead of the initial establishment of the C8′ stereocenter. The alkene can be derived from **4** by reduction, elimination and bromination, avoiding the spare manipulation of protection and deprotection.

Under optimized reaction conditions, diol derived from **4** underwent mesylation and elimination (Et_3N, MsCl, toluene, 0 °C) in one pot, and subsequential bromination (LiBr, DMF, 40 °C) to afford an inseparable mixture of bromo alkenes [terminal:internal (trisubstituted) = 1.8:1] on the decagram scale. Using Shenvi's protocol for olefin isomerization,[23] terminal olefin **30** was converted to trisubstituted olefin **25**. To avoid the undesired halogen exchange (Br → Cl), we employed Co(Sal$^{t\mathrm{Bu}}$, $^{t\mathrm{Bu}}$)Br as a catalyst for olefin isomerization instead of commonly used Co(Sal$^{t\mathrm{Bu},t\mathrm{Bu}}$)Cl. With a large quality of **25** in hand, we directed our attention to intermolecular [2+2] cycloaddition to obtain α-arylcyclobutanone **32**. Brown and co-workers have developed a method for Lewis acid-promoted [2+2] cycloaddition with aryl ketenes, which provided a solution to the limit of [2+2] cycloaddition reactions between poorly reactive and unstable monosubstituted aryl ketenes with alkenes.[24] To our delight, the desired adduct **32** was obtained with high diastereoselectivity using this protocol (Scheme 5), but the conversion rate was found to be dissatisfactory (less than 10%), in spite of our attempts to condition optimization, due to the instability of monosubstituted aryl ketenes and product inhibition.[25]



Scheme 5. Construction of α-arylcyclobutanone **32** through ketene-based [2+2] cycloaddition.

Table 1: Optimization of the keteniminium salt based intermolecular [2+2] cycloaddition reaction.



Entry[a]	Conditions	Yield [%][b] 32	34
1	2,4,6-Collidine, 22 °C to 60 °C, DCE	12	25
2	2,4,6-Collidine, −40 °C to 0 °C, DCE	35	13
3	2-F-Pyridine, −40 °C to 0 °C, DCE	51	16
4	2-Cl-Pyridine, −40 °C to 0 °C, DCE	47	15
5	3-Cl-Pyridine, −40 °C to 0 °C, DCE	45	17
6	*i*Pr$_2$NEt, −40 °C to 0 °C, DCE	0	0
7	DTBMP, −40 °C to 0 °C, DCE	13	21
8	2-F-Pyridine, −40 °C to 0 °C, CH_2Cl_2	37	17
9	2-F-Pyridine, −40 °C to 0 °C, toluene	28	16
10	2-F-Pyridine, −40 °C to −10 °C, DCE	74	14

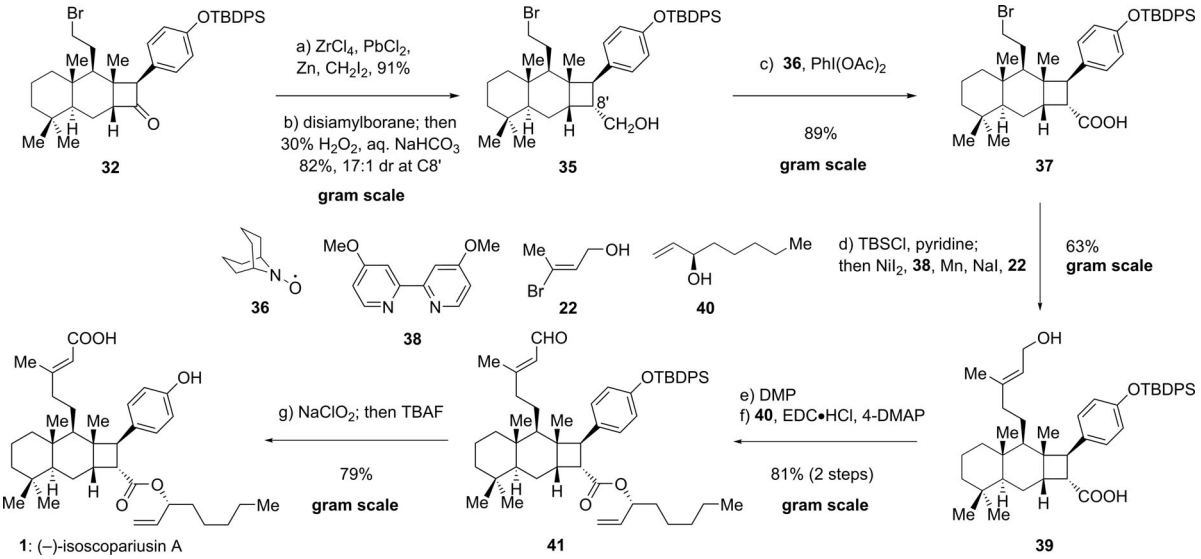
[a] Reagents and conditions: **33** (1.2 equiv), base (1.2 equiv), Tf_2O (1.1 equiv), indicated solvent (0.12 M) at the indicated temperature for 12–30 h. [b] Isolated yield.

An alternative solution to the problem of cycloaddition with unstable or unreactive ketenes and product inhibition is the chemistry of keteniminium salts.[26] However, it still remains a challenge to realize intermolecular [2+2] cycloaddition between a keteniminium salt and trisubstituted alkene to form α-arylcyclobutanones. As illustrated previously, once the first step occurs, due to the stabilization of the tertiary cation and the steric hindrance, the C–N bond of the enamine tends to twist and the cation is rearranged or undergoes β-elimination instead of the four-membered ring formation.[27] In spite of this, we envisaged that some optimized conditions that can stabilize the tertiary cation may work on the issue. Interestingly, under Ghosez's conditions (entry 1 in Table 1),[27d,e] the rearranged and elimination adduct **34** was obtained in 25% yield, and a small ratio for the desired product **32** was also observed. Encouraged by the result, we continued to investigate other reaction conditions. Given the instability of the intermediate **34a**, a lower temperature (−40 °C to 0 °C) was adopted, which led to an improved yield for **32**. Further study on the influences of different bases demonstrated that 2-fluoropyridine behaved in a more superior way compared to 2-chloropyridine, 3-chloropyridine, and so on. Solvent effects on the reaction were also studied and 1,2-dichloroethane (DCE) showed the best performance. Under the optimized conditions (entry 10), the [2+2] cycloaddition proceeded smoothly on a three-gram scale to deliver **32** (74% yield) with the desired stereoselectivity. This finding sheds a new light on the chemistry of keteniminium salts in the intermolecular [2+2] cycloaddition of poly-substituted alkenes.

Completion of the Gram-scale Synthesis and Stereochemical Assignment of (−)-Isoscopariusin A

As illustrated in Scheme 6, carbonyl methylenation of **32** using the Jamison modification of Taikai-Utimoto protocol,[28] followed by selective hydroboration-oxidation using Sia_2BH/H_2O_2 conditions, afforded alcohol **35** with superior selectivity (17:1 dr at C8′). Treatment of **35** with $PhI(OAc)_2$ and a catalytic amount of ABNO (**36**) afforded carboxylic acid **37** in 89% yield.[29] In situ TBDPS protection of carboxylic acid followed by nickel-catalyzed cross-coupling with (*E*)-3-bromobut-2-en-1-ol **21** under the Weix's conditions[30] furnished the desired *E*-product **39** in moderate yield, which overcame the cross-coupling reaction's limited compatibility with carboxylic acid. Oxidation of allylic alcohol to aldehyde, followed by condensation with the chiral fatty alcohol **40**,[31] furnished the ester **41** with good overall efficiency. Lindgren-Krauss-Pinnick oxidation and TBAF removal of the TBDPS protective group in one pot rendered **1** in 79% yield. Over 1 g of synthetic **1** was prepared through this route, every reaction in which can be reliably carried out on a gram scale. The NMR data, specific rotation, and CD spectrum of **1** were in full agreement with those obtained for the authentic natural sample.

In a similar protocol, **42**, the stereoisomer at C3″ of **1**, was also synthesized from **39** (see the Supporting Information), whose NMR spectrum indicated obvious differences at C3″ compared with **1**, which provided an unambiguous evidence for the stereochemical assignment of (−)-isoscopariusin A. Thus, the absolute configuration of the natural (−)-isoscopariusin A was determined to be 5*S*,7*S*,8*R*,9*R*,10*S*,13*E*,7′*S*,8′*R*,3″*R*. Given that some natural producs may not be enantiopure,[32] or have similar chemical structures from two different sources,[33] the chemical syn-



Scheme 6. Completion of the synthesis of **1** on a gram scale.

thesis of (−)-isoscopariusin A unequivocally resolves the stereochemistry and reveals the enantiopure nature of the natural isoscopariusin A.

The Immunosuppressive Activity of (−)-Isoscopariusin A (1)

With an adequate amount of the synthetic (−)-isoscopariusin A in hand, we evaluated the immunosuppressive activity of **1** against the proliferation of T and B lymphocytes in vitro with cyclosporin A (CsA) as the positive control (Table 2). **1** showed significantly inhibitory activity against ConA-induced T-cell proliferation (IC_{50} value of 0.68 μM) and moderate activity against LPS-induced B-cell proliferation (IC_{50} value of 13.81 μM), which suggested immunosuppressive selectivity on T lymphocytes. As far as we know, **1** is a T lymphocyte-selective immunosuppressive meroditerpenoid possessing an unprecedented 6/6/4 tricyclic core, which implies a possible different mechanism of action.

Table 2: Immunosuppressive effect of **1** on murine lymphocyte proliferation induced by ConA (5 μg mL^{-1}) or LPS (10 μg mL^{-1}).[a]

cmpd	CC_{50} [μM]	ConA-induced T-cell proliferation		LPS-induced B-cell proliferation	
		IC_{50} [μM]	SI	IC_{50} [μM]	SI
1	19.65	0.68	28.90	13.81	1.42
CsA	4.09	0.02	204.50	0.70	5.84

[a] CC_{50}, the cytotoxic concentration of the compound that reduces cell viability by 50%; IC_{50}, the inhibitory concentration of the compound that reduces cell proliferation by 50%; Selective Index (SI) = CC_{50}/IC_{50}.

Conclusion

In conclusion, an unprecedented meroditerpenoid, (−)-isoscopariusin A (**1**), was obtained in low abundance from *I. scoparius*, featuring a 6/6/4 tricyclic carbon skeleton and exhibiting potent and selective inhibition of T-cell proliferation. A concise and efficient synthesis of **1** was achieved from commercially available (+)-sclareolide in 12 steps on a gram scale, thereby clarifying the complete assignment of its relative and absolute stereochemistry. The synthesis exhibited the following features: (a) trisubstituted alkenes, the precursors for the [2+2] cycloaddition reaction, prepared through two approaches featuring Negishi coupling and catalytic olefin isomerization, respectively, (b) intermolecular [2+2] cycloaddition of keteniminium salt with trisubstituted alkenes for the construction of α-arylcyclobutanones, and face-selective homologation, which were developed to install four consecutive stereocenters for the key intermediate **35**, and (c) nickel-catalyzed cross-electrophile coupling of vinyl bromide with alkyl bromide, which was applied to deliver the late intermediate **39**. These endeavors pave the way for further structural modification and biological studies of this potential and structurally fascinating class of immunosuppressive agents.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: bioactivity · cyclobutane · natural products · scalable synthesis · structure elucidation

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Research Articles

Total Synthesis

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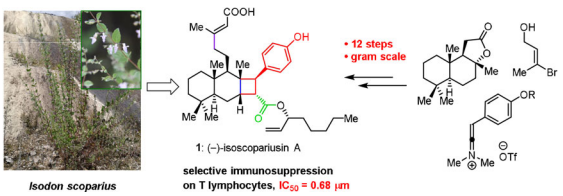
(−)-Isoscopariusin A, a Naturally Occurring Immunosuppressive Meroditerpenoid: Structure Elucidation and Scalable Chemical Synthesis



Reported herein is the isolation, structure determination of (−)-isoscopariusin A by spectroscopic analysis and concise chemical synthesis. The unprecedented meroditerpenoid bears a 6/6/4 tricyclic carbon skeleton with seven continuous stereocenters, and exhibits selective inhibition of T-cell proliferation. A gram-scale synthesis was achieved in 12 steps from (+)-sclareolide.