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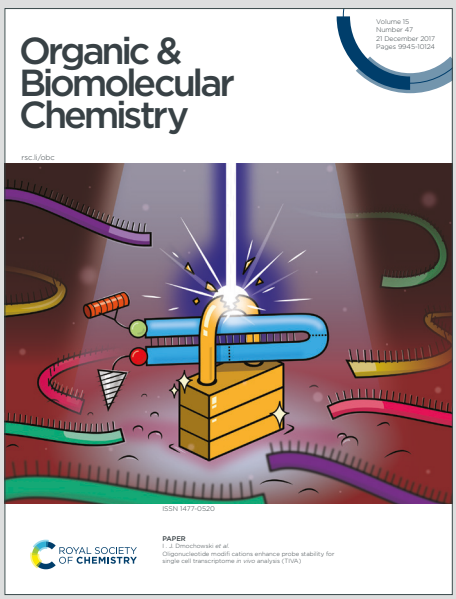

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Total Syntheses of several Iridolactones and the Putative Structure of Noriridoid Scholarein A: An Intramolecular Pauson-Khand Reaction based One-stop Synthetic Solution

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A simple and general approach towards the total syntheses of several iridolactones such as (±)-boschnialactone, (±)-7-*epi*-boschnialactone, (±)-teucriumlactone, (±)-iridomyrmecin, (±)-isoboonein, (±)-7-*epi*-argyol, (±)-scabrol A, (±)-7-*epi*-scabrol A, (±)-patriscabrol as well as the putative structure of scholarein A is delineated. The synthetic strategy features a diastereoselective intramolecular Pauson-Khand reaction (IPKR) to construct the iridoid framework followed by some strategic synthetic manipulations to access the targeted monoterpenes including those having diverse oxy-functionalization pattern and with 3-5 contiguous stereogenic centre in a highly stereocontrolled manner. Also, the present endeavour constitutes the first total synthesis of scabrol A.

Introduction

Iridoids represents one of the most prevalent family of monoterpenoids with more than 300 members already inventoried[1] ever since the report of the first member, iridomyrmecin in the late 1940's.[2] Existing either in the glycosidic or non-glycosidic form, these natural products are the vital components of the medicinal plants used in traditional medicinal practice exhibiting wide array of bioactivities ranging from antiviral, antibacterial, anti-inflammatory, antitumor and cardiovascular activity among others.[3,4] Also, iridoids have been found to be attractants of butterflies and cats as well as exhibit defensive function against their predators.[5,6] Their commercial importance in agricultural pest management is further augmented by their ability to act as sex pheromones against agricultural significant species of aphids.[7] While, from structural perspective iridoids manifest a confined cyclopenta[c]pyran scaffold as exemplified through some distinct members of this family captured in **Figure 1**. However, it is the attendant stereochemical intricacies and the varied oxygenation pattern generally in the cis-fused confined bicyclic framework that renders them as attractive targets for total synthesis.

Owing to their interesting biological and structural attributes iridoids have garnered immense worldwide attention both from biologists and chemists.[3,4,8] Numerous synthetic approaches for elegant access to the iridolactones has been reported, a majority of which were highlighted by us in our recently disclosed approach towards the synthesis of iridoid framework.[9] There are few synthesis which deserve special mention and the list includes, Suh et al. synthesis of a natural iridoid *via* an intramolecular Pd(0) catalyzed allylic-alkylation and transesterification sequence,[10] Lupton and co-workers strategy to access the iridoid framework via NHC catalyzed rearrangement of α, β-unsaturated enol ester,[11] and the very recent Chakraborty et al. reported Ti(III)-mediated reductive epoxide opening-cyclization sequence for accessing iridolactones.[12]

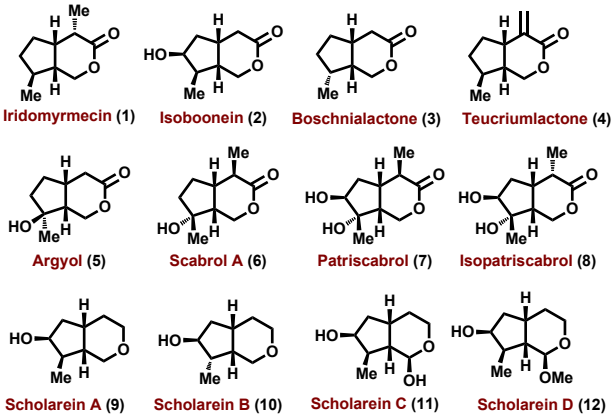

Figure 1. Representative examples of iridoid monoterpenes.

Despite several strategies reported in the literature we comprehended there are very few synthesis which addresses the diverse oxy-functionality pattern manifested on the cyclopentane ring of the iridoid framework.[8f,10,13] Henceforth, there still exists the necessity to develop more efficient and cost economical synthetic approach to access iridoids with relatively higher degree of oxygenation through a unified strategy. And therefore, in view of our ongoing interest[9] in the synthesis of iridoids we were motivated to demonstrate the adaptation of

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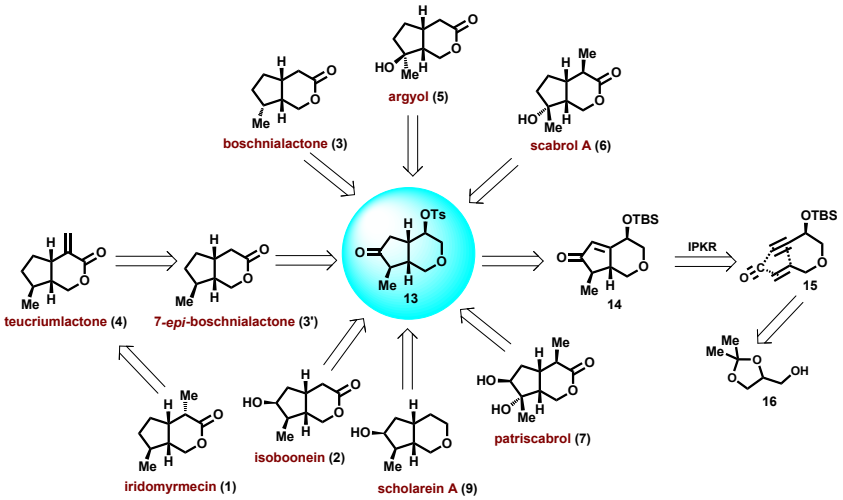


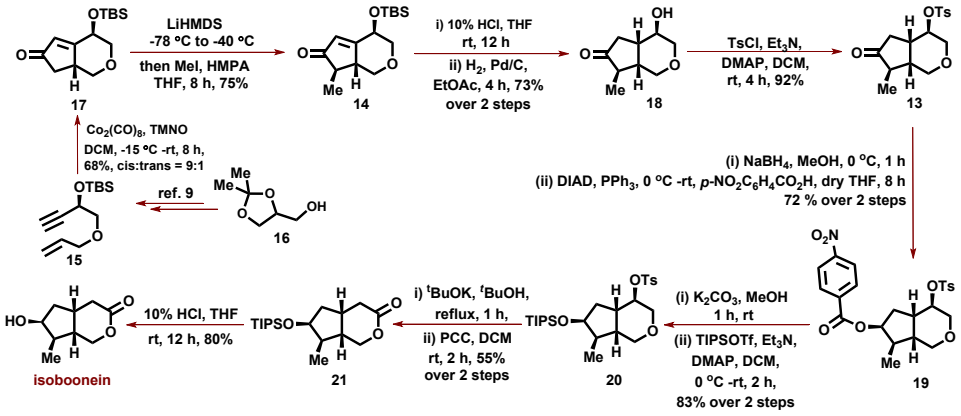
Scheme 1. Retrosynthetic strategy for accessing iridoids **1-9**.

our recently disclosed de novo approach utilizing an intramolecular Pauson-Khand reaction (IPKR) as the key step to access ten iridoids in a stereocontrolled manner, emanating from a very cheap and readily accessible starting material like solketal.

Results and discussion

Adoption of a divergent approach from a common intermediate for accessing the targeted monoterpenoids we believed would be ideal in terms of demonstrating the generality and flexibility of the synthesis. Therefore in this context, the retrosynthetic plan we envisaged for the synthesis of iridoids (**1**-**9**) is as captured in Scheme 1. The bicyclic ether **13** embodying the iridoid framework and having carbonyl functionality at the C_6 and tosylate at C_4 position was expected to serve as a potential intermediate. Exploitation of the C_6 carbonyl group in **13** as the functional group handle was anticipated to offer the other desired functionalization of the cyclopentane ring in context of the targeted natural products (**1**-**9**) while the C_4 tosylate in the tetrahydropyran ring was planned to be manipulated to the δ-lactone ring or simply jettisoned in context of scholarein A (**9**). Moreover, entry to one iridoid could serve as the key for accessing other natural products, for instance synthesis of 7-*epi*-boschnialactone (**3'**) could serve as a precursor to furnish first teucriumlactone (**4**) and subsequently iridomyrmecin (**1**). While entry to the crucial intermediate **13** was planned through our recently reported[9] diastereoselective IPKR on silyl protected enyne ether (**15**) to initially arrive at **14** and subsequently **13** through a couple of synthetic intervention. Whereas, the synthesis of **15** could be traced down from the very cheap and commercially available solketal (**16**).[9]

Scheme 2. Total synthesis of isoboonein **2**



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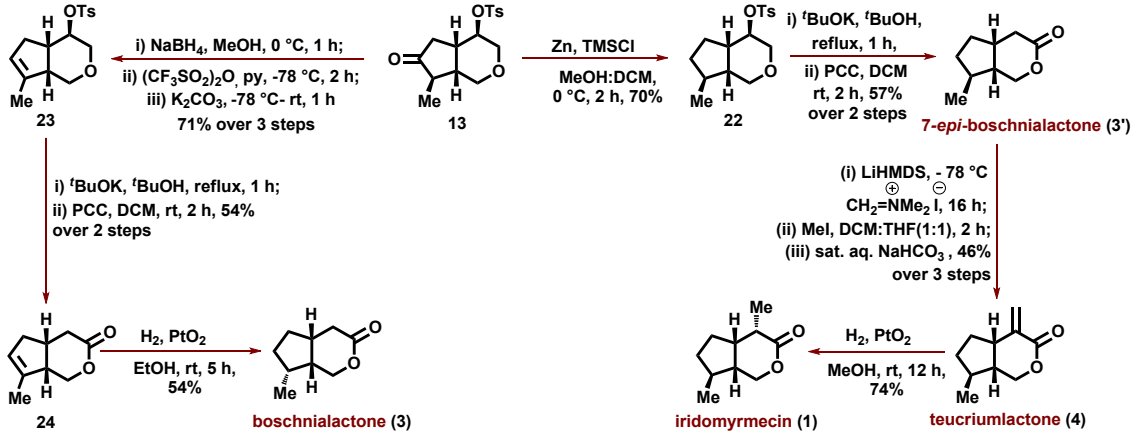

Scheme 3. Synthesis of iridoids **1**, **3**, **4** and epimeric iridoid **3'**.

For operationalization of the proposed retrosynthetic plan outlined in Scheme 1, we first choose isoboonein as the target for total synthesis. In this context, the enyne ether **15** was subjected to our standardized IPKR condition[9] to arrive at **17** with excellent diastereoselectivity (*cis:trans* = 9:1). Elaboration of **17** to **14** via stereoselective methylation and then subsequent silyl deprotection followed by highly stereoselective enone double bond reduction using 10% Pd/C smoothly furnished the bicyclic hydroxy ketone **18**. Further, tosylation of **18** under routine condition readily delivered the key intermediate **13** in excellent yield. With access to **13**, it was matter of reducing the C_6 carbonyl group and manipulating the tosylate group in the tetrahydropyran ring to the δ-lactone. To accomplish this task, **13** was subjected to borohydride reduction and to our delight the reaction ended up delivering a single diastereomer but deviant from the desired stereochemistry at the C_6 hydroxyl group in consonance with our earlier observation and by others on similar substrates.[9] Therefore, Mitsonubu protocol[14] was adopted to invert the C_6 -hydroxy group resulting from the borohydride reduction of **13**, from α to β face through formation of *p*-nitrobenzoate derivative **19**. Hydrolysis of **19** with K_2CO_3 in MeOH delivered the alcohol with desired stereochemistry of the C_6 -hydroxy group in good yield which we opted to protect as the TIPS ether to arrive at **20**. With **20** in hand, the next task was to eliminate the C_4-tosylate group in the tetrahydropyran ring and oxidize the resultant dihydropyran to access the δ-lactone. Towards this goal, subjection of **20** initially to ^{t}BuOK in refluxing ^{t}BuOH facilitated the desired elimination and then exposure of the crude eliminated product to PCC smoothly delivered the desired TIPS protected bicyclic lactone **21**. Eventually, TIPS deprotection in **21** using 10% HCl in THF led to the natural iridolactone isoboonein (**2**) in good yield. The NMR spectral data of the synthetic **2** was found to identical with that reported for the natural isoboonein,[15] thereby confirming the accomplishment of its total synthesis.

After accomplishing the synthesis of natural product **2** attention was then turned toward demonstrating the accessibility of iridoids **1**, **3** and **4** from the key intermediate **13** (Scheme 3) to magnify the divergent nature of the proposed synthetic plan. Therefore, to accomplish the synthesis of iridoid **1** and **4**, the intermediate **13** as delineated in Scheme 3 was first subjected to a Zn/TMSCl mediated Clemmensen reduction[16] to arrive at **22**. Then, repetition of our 2-step synthetic manipulation of the C_4-tosylate group in **22** to the δ-lactone as described in Scheme 2, offered C_7-epimer of boschnialactone (**3'**) in satisfactory yield having spectroscopic data similar to reported by others.[17] Next, from this epimeric natural product (**3'**) it was just a matter of introducing the exocyclic methylene at C_4 position for acquisition of natural product **4** and subsequently **1** through stereoselective exocyclic double bond reduction from the *exo* face. For this task, among the various options for doing the C_4 methylenation we indeed prefer to choose the Eschenmoser[18] protocol to access teucriumlactone (**4**) through three step process in a single pot operation. Thereafter, subsequent reduction of **4** using Adam's catalyst in presence of H_2 gas[19] effortlessly delivered iridomyrmecin (**1**) in a stereoselective fashion. The NMR spectral data of the synthetic **1** and **4** were found to exhibit close resemblance to that reported for the natural products,[2,20] thereby confirming the accomplishment of their total synthesis.

Further, in context of boschnialactone (**3**) the synthetic demand was to epimerize the C_7-Me group in the key intermediate **13** and in view of the presence of adjacent C_7 carbonyl group the task was anticipated to be easily achievable.

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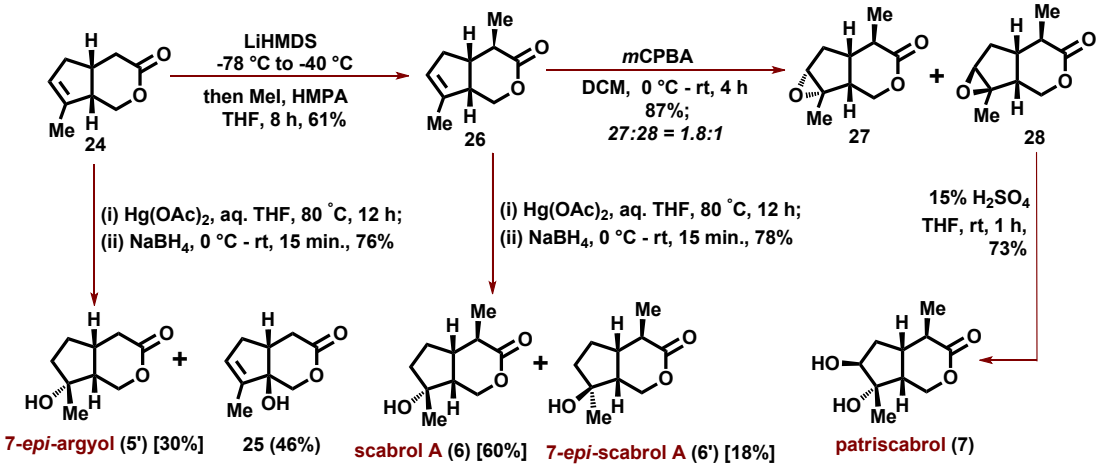
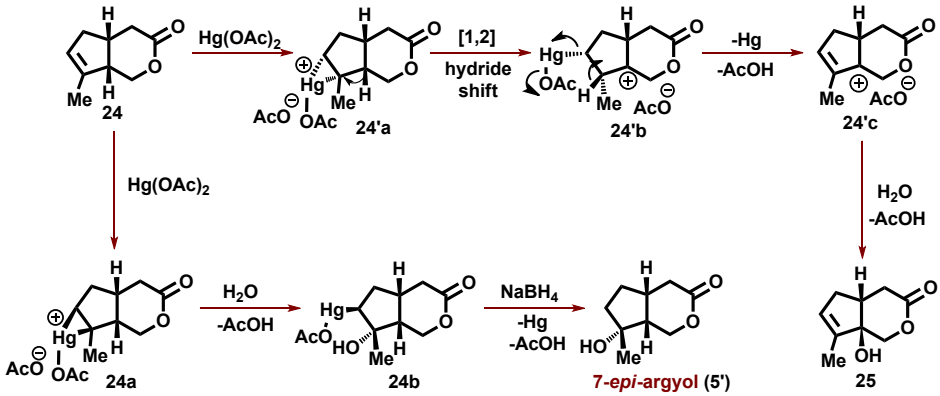


Scheme 4. Synthesis of **5′**, **6**, **6′** and **7**.

However, all our efforts to do the desired epimerization under several base catalyzed conditions proved to be non-rewarding, thereby forcing us to adopt an alternate approach as highlighted in Scheme 3. The problem was circumvented through a stereoselective borohydride reduction of the C_6 carbonyl group and subsequent elimination of the resultant alcohol in a regioselective fashion to arrive at bicyclic olefin **23**. Then the elaboration of **23** *via* a 2 step synthetic intervention to the bicyclic lactone **24** followed by stereoselective olefin double bond reduction in **24** employing Adam's catalyst in presence of H_2 gas furnished the desired synthetic natural product boschnialactone (**3**) with NMR spectral signature similar to that of the isolated natural product[21] thereby confirming its total synthesis.

In our synthetic journey, we next planned to embark on the synthesis of iridoids **5**-**7** in view of accessibility to bicyclic lactone intermediate **24.** Towards this goal as delineated in Scheme 4, first to access natural iridoid **5** and **6**, the task of olefinic double bond hydration in **24** and **24** derived **26** in a Markownikov's fashion was undertaken.[22] Initially, **24** was subjected to oxymercuration using $Hg(OAc)_2$ in refluxing aq. THF and then demercurated to surprisingly arrive at an easily separable mixture of unexpected **25** as the major product and the C_7 epimer of natural iridoid argyol (**5′**) instead of **5**, as the minor product of the reaction. The formation of **25** could be rationalized through a tentative mechanism as highlighted in Scheme 5. Mercuration of of the double bond in **24** from the endo face is presumed to offer first the mercurinium ion **24'a** which then undergoes a 1,2-hydride shift to form the carbocation **24'b**. Thereafter, a spontaneous E2 elimination in **24'b** could be accounted for the formation of a more stable allylic carbocation at C_{7a} position in **24'c**. Eventually the nucleophilic attack of H_2O in **24'c** at C_{7a} position from the *exo* face could be attributed for formation of **25**. On the other hand,

Scheme 5. A plausible mechanism for the formation of **25** and **5′** from **24**.



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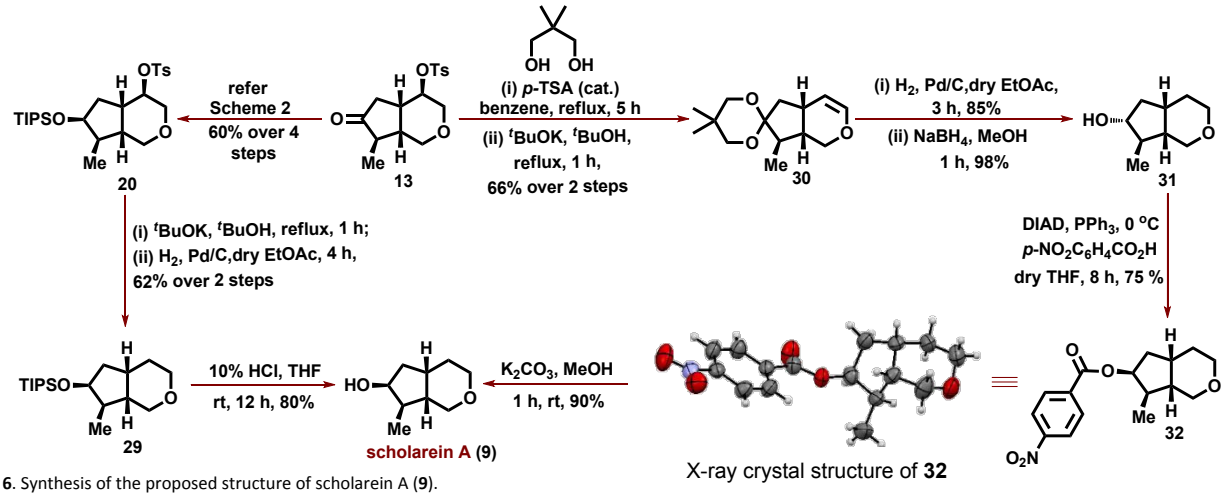

Scheme 6. Synthesis of the proposed structure of scholarein A (**9**).

the oxymercuration on **24** (Scheme 5) from a completely opposite face and then borohydride mediated demercuration could be attributed for formation of **5'**. Interestingly, exposure of **26** (derived via a kinetically controlled methylation on **24**) to similar oxymercuration-demercuration reaction condition milieu to our delight offered the desired natural product scabrol A (**6**) as the predominant product along with its C_7 epimer (**6'**) as the minor product (Scheme 4). The NMR spectral data of the synthetic scabrol A (**6**) was found to exhibit close resemblance to that reported for the natural product[23] thereby culminating in the first total synthesis of scabrol A.

On the other hand to access iridoid natural product **7**, the intermediate **26** was subjected to an *m*CPBA mediated epoxidation to arrive at an easily separable mixture of α and β epoxide, **27** and **28** respectively, albeit with the desired diastereomer **28** as the minor product. Nevertheless, with **28** in hand it was just a matter of acid catalyzed hydrolysis of the epoxide[13c] to arrive at the synthetic patriscabrol **7** in good yield. The NMR spectral data of our synthetic sample was in close agreement with that reported earlier[13c] thereby confirming the accomplishment of its total synthesis.

Lastly, the task of synthesizing noriridoid scholarein A (**9**) was taken in hand and to accomplish its synthesis again the intermediate **13** proved to be the ideal starting material. However, in context of **9** the expulsion of the C_4 tosylate group in **13** turned out to be a tricky proposition in the presence of C_6 carbonyl group therefore two alternative routes as depicted in Scheme 6 were explored to access **9**. Through the first route, the already synthesized intermediate **20** in context of isoboonein was exploited to access scholarein A (**9**). Base mediated elimination of the tosylate group in **20** followed by reduction of the resultant dihydropyran ring afforded **29** in good yield which on TIPS deprotection of the C_6 hydroxy group smoothly furnished the targeted natural product.

Alternatively, the natural product was also accessed via **30** which resulted from the cyclic ketal protection on **13** followed by base mediated tosyl elimination (Scheme 6). Thereafter, the catalytic hydrogenation of the dihydropyran ring in **30** over extended duration not only reduced the dihydropyran ring but also deprotected the C_6 ketal to offer the unmasked carbonyl group which on borohydride reduction offered **31** in excellent yield albeit with undesired stereochemistry of the C_6-OH group. Nevertheless, exposure of **31** to the typical Mitsonubu reaction condition[14] using *p*-nitrobenzoic acid as the nucleophile offered the crystalline *p*-nitrobenzoate derivate **32** in good yield. Single crystal X-ray diffraction studies of **32**[24] unambiguously secured the desired stereochemistry of all its stereogenic centres. Then, it was just a matter of hydrolyzing **32** to accomplish the synthesis of **9**. However, we were taken by surprise when the comparison of the NMR spectral data of our synthetic scholarein A (**9**) indicated significant mismatch with that reported for the natural product.[25] However, on the contrary our NMR data was in close agreement with that of another synthetic scholarein A, reported by others (refer Supp. Information for spectral comparison).[26] While the earlier reports hasn't commented anything about this mismatch,[26] but on the basis of our unambigous synthetic exercise involving X-ray crystal structure analysis of the precusor (**32**) leading to the natural product we suggest that there has been error in the reported structure of scholarein A (**9**) and hence there lies the need for structural revision of scholarein A (**9**).[27] Efforts are underway in our laboratory to synthesize the other possible diastereomer of the proposed structure of the natural product and come up with the revised structure.

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Conclusions

In summary, we have successfully demonstrated though in racemic fashion, a general and simple route to access quite a few iridoids including those having higher oxygenation pattern commencing from very cheap starting material like solketal. A quick entry to the iridoid framework *via* a diastereoselective IPKR followed by some strategic synthetic interventions enabled access to isoboonein, boschnialactone, 7-*epi*-boschnialactone, teucriumlactone, iridomyrmecin, 7-*epi*-argyol, scabrol A, 7-*epi*- scabrol A, patriscabrol and the proposed structure of scholarein A in a stereocontrolled and divergent fashion. Also, the present synthesis of scabrol A happens to be the first total synthesis in the literature for the natural product. Further, efforts are underway to demystify the structure of scholarein A and expand the scope of the approach for accomplishing the synthesis of more complex iridoids. Also, development of an asymmetric version of the approach is under exploration which shall be disclosed soon.

Experimental Section

General Information: All the reagents were purchased from Sigma-Aldrich and other commercial suppliers and used without further purification. While most of the desired solvents supplied by commercial suppliers were dried using the standard drying procedures.[28] All non-aqueous reactions were executed under nitrogen atmosphere. The ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz Bruker spectrometer respectively using TMS as an internal standard. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet/pentet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, dqd = doublet of quartet of doublet and m = multiplet. The chemical shifts are reported as δ values (ppm) and the coupling constants (*J*) values are reported in Hz. High Resolution Mass Spectra (HRMS) were obtained using electron spray ionization (ESI) technique and TOF as mass analyzer. IR spectra were recorded on a Bruker FT/IR-460 Plus spectrometer. Reactions monitoring were done using precoated SiO_2-gel GF254 glass TLC plates while spot visualizations were done under UV light and spot developing stains like *p*-anisaldehyde or $KMnO_4$. Purifications were done using column chromatography with 100-200 mesh size SiO_2-gel as the stationary phase. Compounds **13**-**15**, **17, 18** and **30** were synthesized as per our earlier reported procedure.[9]

***rel-(4R,4aS,6R,7R,7aR)-7-methyl-4-(tosyloxy)octahydrocyclopenta[c]pyran-6-yl 4-nitrobenzoate (19)*:** To stirred solution of **13** (500 mg, 1.54 mmol) in dry MeOH (5 mL) at 0 ˚C, $NaBH_4$ (88 mg, 2.32 mmol) was added. The reaction mixture was then allowed to warm to room temperature and stirred for another 1 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. After aqueous work-up followed by extraction with EtOAc (3 × 15 mL), the organic phase was dried over Na_2SO_4 and then subjected to removal of solvent under reduced pressure to arrive at the crude reduced product (450 mg) as a colourless oil, which was found to be pure enough through NMR spectral analysis to be used in the next step.

To an ice cold solution of DIAD (1.08 mL, 5.52 mmol, 4 equiv.) at 0 °C in dry THF (5 mL), PPh_3 (2.89 g, 11.03 mmol, 8 equiv.) was added and stirred for 10 min. thereafter a solution of the crude alcohol (450 mg, 1.38 mmol) in dry THF (1.5 mL) obtained from the above step was added at same temperature. Subsequently, after another 10 min. *p*-nitrobenzoic acid (4.61 g, 27.57 mmol, 20 equiv.) was added and the mixture was allowed to warm to rt and continued stirring for another 8 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with EtOAc (3 × 25 mL). Drying of the organic phase over Na_2SO_4 and then solvent removal under reduced pressure gave a solid residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (8:2) as the eluent to access the *p*-nitrobenzoate derivative **19** (525 mg, 72% yield over 2 steps) as white solid. IR (neat): ν_{max} 2917, 2850, 1721, 1599, 1349, 1274, 1176, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 5.40 (td, J_1 = 7.0 Hz; J_2 = 3.0 Hz, 1H), 4.24 (td, J_1 = 9.0 Hz; J_2 = 5.0 Hz, 1H), 3.88 (dd, J_1 = 11.0 Hz; J_2 = 5.0 Hz, 1H), 3.80 (dd, J_1 = 12.0 Hz; J_2 = 1.0 Hz, 1H), 3.62 (dd, J_1 = 12.0 Hz; J_2 = 4 Hz, 1H), 3.17 (dd, J_1 = 11.0 Hz; J_2 = 10.0 Hz, 1H), 2.46 (s, 3H), 2.37-2.31 (m, 1H), 2.26-2.16 (m, 1H), 2.08-1.98 (m, 2H), 1.85 (ddd, J_1 = 15.0 Hz; J_2 = 8.0 Hz; J_3 = 3.0 Hz, 1H), 0.99 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.93, 150.51, 145.33, 135.66, 133.41, 130.56 (2C), 130.02 (2C), 127.79 (2C), 123.57 (2C), 78.30, 78.23, 68.72, 66.10, 45.45, 40.74, 38.14, 35.80, 21.69, 12.19.

rel-(4R,4aS,6R,7R,7aR)-7-methyl-6-(triisopropylsilyl)oxy)octahydrocyclopenta[c]pyran-4-yl-4-methylbenzenesulfonate (20): To a stirred solution of *p*-nitrobenzoate derivative **19** (500 mg, 1.05 mmol) was added K_2CO_3 (720 mg, 5.25 mmol, 5 equiv.) in MeOH (10 mL)and the mixture was allowed to stir at rt for 1 h until complete consumption of starting material was indicated by TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with EtOAc (3 × 15 mL). Drying of the organic phase over Na_2SO_4 and then solvent removal under reduced pressure gave an oily residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (7:3) as the eluent to access the crude alcohol which was directly used in the next step.

To the cold solution of crude alcohol obtained after hydrolysis of benzoate **19** at 0 ˚C in dry DCM (5 mL) was added Et_3N (1.4 mL, 10.05 mmol, 10 equiv.) followed by sequential addition of TIPSOTf (0.42 mL, 1.58 mmol, 1.5 equiv.) and DMAP (1 mg, 0.01 mmol, 0.01 equiv.). The reaction mixture was then allowed to warm to rt and continued stirring for another 2 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by removing the solvent under reduced pressure and then subjecting the resultant residue to SiO_2-gel column chromatography using hexanes/EtOAc (8:2) as the eluent to arrive at pure TIPS protected bicyclic alcohol **20** (421 mg, 83% yield over 2 steps) as colorless oil. IR (neat): ν_{max} 2943, 1598,

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1464, 1367, 1177, 947, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.23-4.15 (m, 2H), 3.84 (dd, J_1 = 11.0 Hz; J_2 = 5.0 Hz, 1H), 3.73 (dd, J_1 = 12.0 Hz; J_2 = 1.0 Hz, 1H), 3.58 (dd, J_1 = 12.0 Hz; J_2 = 4 Hz, 1H), 3.16 (dd, J_1 = 11.0 Hz; J_2 = 10.0 Hz, 1H), 2.43 (s, 3H), 2.25-2.18 (m, 1H), 1.94-1.80 (m, 2H), 1.74-1.61 (m, 2H), 1.02 (br s, 21H), 0.96 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.88, 133.77, 129.82 (2C), 127.77 (2C), 79.51, 74.32, 68.62, 66.71, 44.55, 40.35, 39.77, 39.38, 21.60, 18.05 (3C), 17.99 (3C), 12.65, 12.28 (3C). HRMS (ESI) m/z calcd for $C_{25}H_{43}O_5SSi$ $(M+H)^+$: 483.2595; found: 483.2597.

rel-(4aR,6R,7R,7aS)-7-methyl-6-(triisopropylsilyl)oxy)-hexahydrocyclopenta[c]pyran-3(1H)-one (21): To a stirred solution of TIPS protected bicyclic alcohol **20** (400 mg, 0.83 mmol) in ^{t}BuOH (4 mL) was added ^{t}BuOK (465 mg, 4.15 mmol, 5 equiv.) at rt. The reaction mixture was then allowed to reflux for 1 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with EtOAc (3 × 15 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude oily residue which was directly used in the next step.

To the cold solution of crude residue obtained from the above reaction in dry DCM (5 mL) at 0 °C, PCC (535 mg, 2.49 mmol, 3 equiv.) was added. The reaction mixture was then allowed to warm to rt and stirred for another 2 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by removing the solvent under reduced pressure and then subjecting the resultant residue to SiO_2-gel column chromatographic purification using hexanes/EtOAc (9:1) as the eluent to arrive at lactone **21** (148 mg, 55% yield over 2 steps). IR (neat): ν_{max} 2943, 1752, 1462, 1079, 1040, 882, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 4.24 (t, *J* = 3 Hz, 1H), 4.13 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 2.94-2.84 (m, 1H), 2.63 (dd, J_1 = 15 Hz, J_2 = 7 Hz, 1H), 2.35 (dd, J_1 = 15 Hz, J_2 = 4 Hz, 1H), 2.15 (tt, J_1 = 10 Hz, J_2 = 4 Hz, 1H), 2.03 (dd, J_1 = 13 Hz, J_2 = 8 Hz, 1H), 1.89-1.81 (m, 1H), 1.35 (ddd, J_1 = 14 Hz, J_2 = 10 Hz, J_3 = 3 Hz, 1H), 1.06 (br s, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.67, 76.23, 68.74, 42.44, 42.35, 41.89, 34.57, 32.55, 18.14(3C), 18.11(3C), 13.42, 12.48 (3C). HRMS (ESI) m/z calcd for $C_{18}H_{35}O_3Si$ $(M+H)^+$: 327.2350; found: 327.2359.

(±) isoboonein (2): To a stirred solution of lactone **21** (125 mg, 0.38 mmol) in THF (2.5 mL), 10% HCl (2.5 mL) was added at rt and the reaction was allowed to stir for 12 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by quenching it with sat. aq. $NaHCO_3$ solution followed by extraction with EtOAc (3 × 15 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude oily residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (2:8) as the eluent to arrive at the synthetic natural product isoboonein **2** (52 mg, 80% yield) as colorless oil. IR (neat): ν_{max} 2971, 2931, 1734, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (dd, J_1 = 12 Hz, J_2 =4 Hz, 1H), 4.15 (dd, J_1 = 12 Hz, J_2 = 3 Hz, 1H), 4.14-4.13 (m, 1H), 3.00-2.90 (m, 1H)), 2.64 (dd, J_1 = 15 Hz, J_2 = 7 Hz, 1H), 2.38 (dd, J_1 = 15 Hz, J_2 = 4 Hz, 1H), 2.16 (tt, J_1 = 10 Hz, J_2 = 4 Hz, 1H), 2.06 (dd, J_1 = 14 Hz, J_2 = 8 Hz, 1H), 1.92 (dqd, J_1 = 10 Hz, J_2 = 7 Hz, J_3 = 3 Hz, 1H), 1.46 (br s, 1H), 1.42 (ddd, J_1 = 14 Hz, J_2 = 10 Hz, J_3 = 4 Hz, 1H), 1.08 (d, = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.50, 75.61, 68.52, 41.63, 41.54, 41.42, 34.47, 32.62, 12.64. HRMS (ESI) m/z calcd for $C_9H_{15}O_3$ $(M+H)^+$: 171.1016; found: 171.1015.

rel-(4R,4aS,7R,7aS)-7-methyl-6-oxooctahydrocyclopenta[c] pyran-4-yl-4-methylbenzene-sulfonate (22): To a stirred solution of **13** (400 mg, 1.23 mmol) in 4 ml of MeOH and DCM (ratio of 3:1 respectively) containing activated Zn powder (2.4 g, 37 mmol, 30 equiv.) was added TMSCl (4.7 mL, 37 mmol, 30 equiv.) at 0 °C. The reaction was continued stirring for an additional 1.5 h at same temperature until complete consumption of starting material and formation of a new spot was indicated by TLC analysis. The reaction was quenched with $NaHCO_3$ (3.1 g, 37 mmol, 30 equiv.) and allowed to warm to rt over 10 min. followed by addition of sat. aq. NH_4Cl and then extraction in EtOAc (3 × 15 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude oily residue which was subjected to SiO_2-gel column chromatographic purification using hexanes/EtOAc (8:2) as the eluent to arrive at pure **22** (267 mg, 70% yield) as colorless oil. IR (neat): ν_{max} 2952, 2870, 1598, 1463, 1363, 1176, 1099, 957 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 4.28 (td, J_1 = 9 Hz, J_2 = 4 Hz, 1H), 3.83 (dd J_1 = 11 Hz, J_2 = 4 Hz, 1H), 3.64 (dd J_1 = 12 Hz, J_2 = 3 Hz, 1H), 3.54 (dd J_1 = 12 Hz, J_2 = 4 Hz, 1H), 3.20 (dd J_1 = 12 Hz, J_2 = 9 Hz, 1H), 2.45 (s, 3H), 2.14 (ddd, J_1 = 15 Hz, J_2 = 7 Hz, J_3 = 3 Hz, 1H), 1.94-1.78 (m, 2H), 1.68-1.56 (m, 2H), 1.42-1.35 (m, 1H), 1.22-1.10 (m, 1H), 0.93 (d, *J* = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.85, 133.87, 129.83 (2C), 127.81 (2C), 77.97, 68.46, 66.69, 47.82, 43.14, 33.40, 31.35, 26.47, 21.64, 19.71. HRMS (ESI) m/z calcd for $C_{16}H_{23}O_4S$ $(M+H)^+$: 311.1312; found: 311.1315.

(±) 7-epi-boschnialactone (3'): To a stirred solution of tosylate **22** (200 mg, 0.64 mmol.) in ^{t}BuOH (2.5 mL) was added ^{t}BuOK (358 mg, 3.20 mmol, 5 equiv.) at rt. The reaction mixture was then allowed to reflux for 1h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with EtOAc (3 × 15 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude oily residue which was directly used in the next step.

To the cold solution of crude residue obtained from the above step in dry DCM (2.5 mL) at 0 °C, PCC (413 mg, 1.92 mmol, 3 equiv.) was added. The reaction mixture was then allowed to warm to rt and stirred for another 2 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by removing the solvent under reduced pressure and then subjecting the resultant residue to SiO_2-gel column chromatographic purification using hexanes/EtOAc (8:2) as the eluent to arrive at 7-*epi*-boschnialactone **3'** (57 mg, 57% yield over 2 steps). IR (neat): ν_{max} 2952, 1746, 1479, 1387, 1275, 1166, 1037, 969, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (dd, J_1 =

12 Hz, J_2 = 4 Hz, 1H), 4.07 (dd J_1 = 12 Hz, J_2 = 5 Hz, 1H), 2.63-2.53 (m, 2H), 2.34-2.28 (m, 1H), 2.02-1.98 (m, 1H), 1.89-1.73 (m, 3H), 1.26-1.08 (m, 2H), 1.03 (d, J_2 = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.62, 68.89, 44.53, 37.43, 34.76, 34.73, 34.54, 33.33, 18.63. HRMS (ESI) m/z calcd for $C_9H_{15}O_2$ $(M+H)^+$: 155.1067; found: 155.1074.

(±) teucriumlactone (4): To a stirred solution of 7-*epi*-boschnialactone **3'** (50 mg, 0.32 mmol.) in 2.5 mL of dry THF was added LiHMDS (1.0 M in THF, 0.7 mL, 0.65 mmol, 2 equiv.) at -78 °C and the resulting mixture was stirred for 2 h at same temperature. After 2 h, Eschenmoser salt (180 mg, 0.975 mmol, 3 equiv.) was added and the reaction was subsequently allowed to warm to rt over 10 h until complete consumption of starting material and formation of new spot was indicated by TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with EtOAc (3 × 15 mL). Drying of the organic phase over Na_2SO_4 and subsequent removal of solvent under reduced pressure gave a crude residue which was directly used in the next step.

To the cold solution of crude residue obtained from the above step in 2 mL of DCM:THF (1:1) was added MeI (0.1 mL, 1.62 mmol, 5 equiv.) at 0 °C and the resulting mixture was continued stirring for another 2 h at same temperature. After addition of sat. aq. $NaHCO_3$ solution (3 mL) the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was then diluted with water followed by extraction with EtOAc (3 × 15 mL). Drying of the organic phase over Na_2SO_4 and subsequent removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel column chromatographic purification using hexanes/EtOAc (8:2) as the eluent to arrive at the synthetic natural product teucriumlactone **4** (25 mg, 46% over 2 steps). IR (neat): ν_{max} 2953, 1733, 1638, 1460, 1303, 1139, 1083, 935 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (t, J = 1 Hz, 1H), 5.46 (t, J = 1 Hz, 1H), 4.18 (dd, J_1 = 11 Hz, J_2 = 4 Hz, 1H), 4.04 (dd, J_1 = 11 Hz, J_2 = 5 Hz, 1H), 3.14 (dd, J_1 = 18 Hz, J_2 = 10 Hz, 1H), 2.17−2.04 (m, 1H), 1.99−1.80 (m, 3H), 1.48−1.38 (m, 1H), 1.29− 1.16 (m, 1H), 1.08 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.40, 140.41, 124.64, 68.23, 45.37, 41.86, 36.86, 34.92, 33.90, 18.90. HRMS (ESI) m/z calcd for $C_{10}H_{15}O_2$ $(M+H)^+$: 167.1067; found: 167.1067.

(±) iridomyrmecin (1): A solution of teucriumlactone **4** (20 mg, 0.120 mmol.) in MeOH (1.5 mL) was subjected to catalytic hydrogenation using PtO_2 (1.5 mg) under 1 atmosphere H_2 pressure at rt for 12 h until complete consumption of starting material was indicated by TLC analysis. The reaction was worked up by passing it through a short celite bed followed by washing of the celite bed with EtOAc. The combined organic phase were evaporated under vacuum and the resultant crude residue was subjected to SiO_2-gel column chromatographic purification using hexanes/EtOAc (9:1) as the eluent to arrive at the synthetic natural product iridomyrmecin **1** (15 mg, 74% yield).[29] IR (neat): ν_{max} 2925, 1747, 1639, 1455, 1378, 1107, 985 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (dd, J_1 = 12 Hz, J_2 = 3 Hz, 1H), 4.18 (d, J = 12 Hz, 1H), 2.74−2.67 (m, 1H), 2.64-2.55 (m, 1H), 1.91−1.74 (m, 4H), 1.15 (d, J = 7 Hz, 3H), 1.05 (d, J = 6.0 Hz, 3H), 1.11−0.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 176.24, 67.90, 45.44, 41.13, 37.9, 37.30, 34.16, 29.82, 18.39, 12.74. HRMS (ESI) m/z calcd for $C_{10}H_{16}NaO_2$ $(M+Na)^+$: 191.1043; found: 191.1045.

rel-(4R,4aS,7aS)-7-methyl-1,3,4,4a,5,7a-hexahydrocyclo-penta[c]pyran-4-yl-4-methyl- benzenesulfonate (23): To the solution of the reduced product (800 mg, 2.45 mmol) in dry DCM (15 mL) obtained from the borohydride reduction of **13** as per the already described procedure**,** was added pyridine (2.97 mL, 36.75 mmol, 15 equiv.) followed by Tf_2O (3.3 mL, 19.60 mmol, 8 equiv.) at -78 °C. The reaction was further stirred for an additional 1 h at the same temperature. Then after 1 h, K_2CO_3 (6.76 g, 49.0 mmol, 20 equiv.) was added and the reaction was allowed to warm to rt over 1 h, until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by pouring it into chilled water followed by extraction with Et_2O. The organic phase was washed with aq. $CuSO_4$, H_2O and brine, dried over Na_2SO_4 and concentrated in vacuum to arrive at a crude residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (7:3) as the eluent to arrive at the bicyclic olefin **23** (597 mg, 79% yield over 2 steps) as a colorless oil. IR (neat): ν_{max} 2923, 1597, 1445, 1362, 1175, 1095, 959 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 5.31 (br s , 1H), 4.37-4.32 (m, 1H), 3.74-3.65 (m, 3H), 3.33 (dd, J_1 = 12 Hz, J_2 = 8 Hz, 1H), 2.59 (br s, 1H), 2.45 (s, 3H)), 2.38 (ddd, J_1 = 13 Hz, J_2 = 6 Hz, J_3 = 4 Hz, 1H), 2.28-2.20 (m, 1H), 1.98-1.88 (m, 1H), 1.67 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.80, 140.97, 133.78, 129.80 (2C), 127.73 (2C), 124.60, 78.07, 67.73, 66.93, 46.14, 41.87, 33.50, 21.60, 14.61. HRMS (ESI) m/z calcd for $C_{16}H_{20}NaO_4S$ $(M+Na)^+$: 331.0975; found: 331.0982.

rel-(4aR,7aS)-7-methyl-1,4a,5,7a-tetrahydrocyclopenta[c] pyran-3(4H)-one (24): To a stirred solution of tosylate **23** (600 mg, 1.95 mmol) in ^{t}BuOH (5 mL) was added ^{t}BuOK (1.09 g, 9.75 mmol, 5 equiv.) at rt. The reaction mixture was then allowed to reflux for 1 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with EtOAc (3 × 20 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude oily residue which was directly used in the next step.

To the cold solution of crude residue obtained from the above reaction in dry DCM (5 mL) at 0 °C, PCC (1.26 g, 5.85 mmol, 3 equiv.) was added. The reaction mixture was then allowed to warm to room temperature and stirred for another 2 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by removing the solvent under reduced pressure and then subjecting the resultant residue to SiO_2-gel column chromatographic purification using hexanes/EtOAc (7:3) as the eluent to arrive at lactone **24** (159 mg, 54% yield over 2 steps). IR (neat): ν_{max} 2923, 1743, 1632, 1451, 1301, 1239, 1142, 1074, 981 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (br s, 1H), 4.32 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 4.25 (dd J_1 = 12 Hz, J_2 = 4 Hz, 1H), 3.00-2.91 (m, 2H), 2.76-2.68 (m, 1H), 2.64 (dd, J_1 = 15 Hz, J_2 = 7 Hz, 1H), 2.38 (dd, J_1 = 15 Hz, J_2 = 4 Hz, 1H), 2.13-2.06 (m, 1H), 1.69 (d, J = 2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.37, 136.72, 126.78, 67.50, 47.37, 39.63, 35.80, 32.70, 14.51.

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HRMS (ESI) m/z calcd for $C_9H_{13}O_2$ $(M+H)^+$: 153.0910; found: 153.0918.

(±) boschnialactone (3): The lactone **24** (25 mg, 0.164 mmol) in EtOH (1 mL) was subjected to catalytic hydrogenation using PtO_2 (2 mg) under 1 atmosphere H_2 pressure at rt for 5 h until complete consumption of starting material was indicated by TLC analysis. The reaction was worked up by passing it through a short celite bed followed by washing of the celite bed with EtOAc. The combined organic phase was evaporated under vacuum and the resultant crude residue was subjected to SiO_2-gel column chromatographic purification using hexanes/EtOAc (9:1) as the eluent to arrive at the synthetic natural product boschnialactone **3** (18 mg, 70% yield). IR (neat): ν_{max} 2924, 1737, 1641, 1461, 1379, 1241, 1188, 1056, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (dd, J_1 = 12 Hz, J_2 = 6 Hz, 1H), 4.12 (dd J_1 = 12 Hz, J_2 = 9 Hz, 1H), 2.64-2.56 (m, 2H), 2.42 (dq, J_1 = 9 Hz, J_2 = 6 Hz, 1H), 2.28 (dd, J_1 = 17 Hz, J_2 = 11 Hz, 1H), 2.20-2.12 (m, 1H), 1.94-1.85 (m, 1H), 1.77-1.69 (m, 1H), 1.53-1.47 (m, 1H), 1.35 (dq, J_1 = 12 Hz, J_2 = 7 Hz, 1H), 1.03 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.88, 67.52, 39.63, 37.33, 35.06, 34.83, 32.82, 32.79, 14.64. HRMS (ESI) m/z calcd for $C_9H_{15}O_2$ $(M+H)^+$: 155.1067; found: 155.1074.

rel-(4aR,7aR)-7a-hydroxy-7-methyl-1,4a,5,7a-tetrahydrocyclopenta [c]pyran-3(4H)-one (25): To a solution of **24** (40 mg, 0.26 mmol) in 2 ml of THF:H_2O (3:1) was added $Hg(OAc)_2$ (248 mg, 0.78 mmol, 3 equiv.) at rt and then subsequently stirred at 80 °C for another 12 h until complete consumption of starting material and formation of a new spot was indicated by TLC analysis. Thereafter, the reaction was cooled to ambient temperature before adding $NaBH_4$ (59 mg, 1.56 mmol, 6 equiv.) and stirred for 15 min. until completion of the reaction was indicated by TLC analysis. The reaction was quenched with sat. aq. NH_4Cl, diluted with H_2O followed by extraction with EtOAc (3 × 10 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel column chromatography to access first **25** (20 mg, 46% yield) as colorless oil and then 7-*epi*-argyol (**5'**) (13 mg, 30%). Spectral data for **25**, IR (neat): ν_{max} 3022, 2923, 1732, 1598, 1360, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64-5.62 (m, 1H), 3.98 (d, J = 12 Hz, 1H), 3.54 (d, J = 12 Hz, 1H), 3.12-3.05 (m, 1H), 2.95 (dd, J_1 = 18 Hz, J_2 = 10 Hz, 1H), 2.73-2.64 (m, 1H), 2.35 (dd, J_1 = 18 Hz, J_2 = 6 Hz, 1H), 2.15 (ddd, J_1 = 17 Hz, J_2 = 4 Hz, J_3 = 2 Hz, 1H), 1.74 (dd, J_1 = 4 Hz, J_2 = 2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 177.12, 137.55, 130.34, 100.78, 64.08, 37.86, 37.67, 37.52, 12.42. HRMS (ESI) m/z calcd for $C_9H_{12}O_3Na$ $(M+Na)^+$: 191.0679; found: 191.0667.

(±)7-epi-argyol (5'): IR (neat): ν_{max} 2924, 1730, 1546, 1198, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (dd, J_1 = 12 Hz, J_2 = 8 Hz, 1H), 4.32 (dd, J_1 = 12 Hz, J_2 = 6 Hz,, 1H), 2.66-2.52 (m, 2H), 2.48 – 2.42 (m, 1H), 2.26 – 2.20 (m, 1H), 2.02 – 1.94 (m, 1H), 1.83 – 1.77 (m, 1H), 1.72 – 1.56 (m, 2H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 173.68, 79.92, 66.56, 46.03, 41.91, 35.17, 34.92, 30.79, 28.00. HRMS (ESI) m/z calcd for $C_9H_{15}O_3$ $(M+H)^+$: 171.1016; found: 171.1017.

rel-(4R,4aS,7aS)-4,7-dimethyl-1,4a,5,7a-tetrahydrocyclopenta [c] pyran-3(4H)-one (26): To a solution of **24** (60 mg, 0.39 mmol) in 1 mL THF was added LiHMDS (1.0 M in THF, 0.80 mL, 0.78 mmol, 2 equiv.) at –78 °C and the resulting mixture was stirred for 4 h at same temperature. After 4 h, MeI (0.12 mL, 1.95 mmol, 5 equiv.), HMPA (0.2 mL) dissolved in 1 mL of dry THF were added and the mixture was subsequently stirred at -78 °C for another 1 h and then allowed to warm to -50 °C and continued stirring for another 1 h until significant formation of a new spot was indicated by the TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with EtOAc (3 × 10 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel column chromatography to access first marginal amount of dimethylated product (9 mg, 14%) followed by the predominant monomethylated bicyclic lactone **26** (40 mg, 61% yield and 73% brsm) and then recovery of slightly unreacted **24** (10 mg). IR (neat): ν_{max} 2924, 1745, 1640, 1546, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39 (br s, 1H), 4.40 (dd, J_1 = 11 Hz, J_2 = 6 Hz, 1H), 3.93 (t, J = 12 Hz, 1H), 3.02 (br s, 1H), 2.73 (dd, J_1 = 16 Hz, J_2 = 8 Hz, 1H), 2.44-2.32 (m, 2H), 2.16 (d, J = 17 Hz, 1H), 1.63 (s, 3H), 1.19 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 175.83, 136.73, 126.19, 68.77, 48.07, 40.91, 38.92, 38.81, 14.68, 14.03. HRMS (ESI) m/z calcd for $C_{10}H_{15}O_2$ $(M+H)^+$: 167.1067; found: 167.1068.

(±) scabrol A (6): To a stirred solution of **26** (40 mg, 0.24 mmol) in 2 ml of THF:H_2O (3:1) was added $Hg(OAc)_2$ (223 mg, 0.72 mmol, 3 equiv.) at rt and then subsequently stirred at 80 °C for another 12 h until complete consumption of starting material and formation of a new spot was indicated by TLC analysis. Thereafter, the reaction was cooled to ambient temperature before adding $NaBH_4$ (54 mg, 1.44 mmol, 6 equiv.) and stirred for 15 min until completion of the reaction was indicated by TLC analysis. The reaction was quenched with sat. aq. NH_4Cl, diluted with H_2O followed by extraction with EtOAc (3 × 10 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel column chromatography to access first scabrol A, **6** (27 mg, 60% yield) as colorless oil and then 7-*epi*-scabrol A (**6'**) (8 mg, 18%). Data for (±) scabrol A, **6**: IR (neat): ν_{max} 3437, 2966, 1726, 1380, 1250, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.42 (t, J = 12 Hz, 1H), 4.33 (dd, J_1 = 12 Hz, J_2 = 7 Hz, 1H), 2.48 (dq, J_1 = 11 Hz, J_2 = 7 Hz, 1H), 2.29 (td, 3.93 (t, J_1 = 11 Hz, J_2 = 7 Hz, 1H), 2.08-1.94 (m, 2H), 1.83-1.78 (m, 1H), 1.73-1.67 (m, 2H), 1.37 (s, 3H), 1.18 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 176.63, 79.58, 65.77, 46.70, 42.56, 42.46, 38.98, 30.08, 27.73, 13.58. HRMS (ESI) m/z calcd for $C_{10}H_{17}O_3$ $(M+H)^+$: 185.1172; found: 185.1173.

(±) 7-epi-scabrol A (6'): IR (neat): ν_{max} 3421, 2972, 1726, 1641, 1179, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.27 (dd, J_1 = 11 Hz, J_2 = 6 Hz, 1H), 3.86 (t, J = 12 Hz, 1H), 2.41-2.25 (m, 4H), 1.76-1.72 (m, 2H), 1.59-1.53 (m, 2H), 1.28 (s, 3H), 1.24 (d, 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.58, 80.54, 66.75, 49.16, 41.69, 39.11, 37.71, 29.79, 23.61, 14.34. HRMS (ESI) m/z calcd for $C_{10}H_{17}O_3$ $(M+H)^+$: 185.1172; found: 185.1174.

rel-(1aS,1bR,5R,5aS,6aS)-1a,5-dimethylhexahydrooxireno-[2',3':4,5]cyclopenta[1,2-c] pyran-4(1aH)-one (27): To a stirred solution of **26** (60 mg, 0.36 mmol) in dry DCM (4 mL) was added

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*m*CPBA (86 mg, 0.5 mmol, 1.4 equiv.) at 0 °C and stirred for 4 h until the consumption of starting material and formation of a new spot was indicated by TLC analysis. The reaction was worked up by quenching it with sat. aq. $NaHCO_3$ followed by extraction with DCM (3× 10 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (1:1) as the eluent to access first the α-epoxide **27** (36 mg, 55% yield) as the predominant product and β-epoxide **28** (20 mg, 31% yield) as the minor product. Data for **27**: IR (neat): ν_{max} 2971, 1732, 1456, 1384, 1167, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (dd, J_1 = 11 Hz, J_2 = 7 Hz, 1H), 4.36 (t, J = 11 Hz, 1H), 3.43 (d, J = 1 Hz, 1H), 2.66 (ddd, J_1 = 11 Hz, J_2 = 10 Hz, J_3 = 7 Hz, 1H), 2.56 – 2.42 (m, 1H), 2.23 – 2.07 (m, 2H), 1.97 (d, J = 13.3 Hz, 1H), 1.41 (s, 3H), 1.13 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.26, 67.66, 67.05, 65.51, 41.77, 41.52, 39.01, 31.56, 16.59, 13.33. HRMS (ESI) m/z calcd for $C_{10}H_{15}O_3$ $(M+H)^+$: 183.1016; found: 183.1017.

rel-(1aR,1bR,5R,5aS,6aR)-1a,5-dimethylhexahydrooxireno [2',3':4,5] cyclopenta[1,2-c] pyran-4(1aH)-one ((28) : Minor product of epoxidation on **26**. IR (neat): ν_{max} 2984, 1732, 1456, 1385, 1261, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.30 (dd, J_1 = 11 Hz, J_2 = 5.0 Hz, 1H), 4.06 (dd, J_1 = 12 Hz, J_2 =11 Hz, 1H), 3.41 (s, 1H), 2.61-2.57 (m, 1H), 2.55 (dd, J_1 = 14 Hz, J_2 =8 Hz, 1H), 2.28 (dq, J_1 = 10 Hz, J_2 = 7 Hz, 1H), 2.00 (dt, J_1 = 18, J_2 =9 Hz, 1H), 1.63 (ddd, J_1 = 14 Hz, J_2 = 7 Hz, J_3 = 1 Hz, 1H), 1.40 (s, 3H), 1.20 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.77, 65.90 , 64.77, 64.54, 43.51, 39.56, 39.50, 35.85, 15.31, 14.39. HRMS (ESI) m/z calcd for $C_{10}H_{15}O_3$ $(M+H)^+$: 183.1016; found: 183.1016.

(±) patriscabrol (7): To a stirred solution of epoxide **28** (15 mg, 0.08 mmol) in 2 mL of THF was added 2.5 mL of 1.5 M H_2SO_4 at 0 °C and the reaction was allowed to warm to rt over 2 h. On completion of the reaction, it was quenched with sat. aq. $NaHCO_3$ followed by extraction with EtOAc (3× 10 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (1:2) to access synthetic patriscabrol, **7** (16 mg, 73%) IR (neat): ν_{max} 2986, 1721, 1461, 1384, 1256, 1183, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (t, J = 12 Hz, 1H), 4.36 (dd, J_1 = 12 Hz, J_2 = 7 Hz, 1H), 3.98 (t, J = 4 Hz, 1H), 2.60 – 2.39 (m, 2H), 2.28 – 2.14 (m, 1H), 1.98-1.95 (m, 2H), 1.37 (s, 3H), 1.18 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ176.71 , 81.21 , 80.66, 65.61, 44.04, 39.53, 38.96, 37.68, 22.35, 13.60. HRMS (ESI) m/z calcd for $C_{10}H_{17}O_4$ $(M+H)^+$: 201.1121; found: 201.1123.

rel-triisopropyl((4aS,6R,7R,7aS)-7-methyloctahydrocyclo-penta[c]pyran-6-yl)oxy)silane (29): To a stirred solution of tosylate **20** (80 mg, 0.16 mmol.) in ^{t}BuOH (2 mL) was added ^{t}BuOK (90 mg, 0.80 mmol, 5 equiv.) at rt. The reaction mixture was then allowed to reflux for 1 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with Et_2O (3 × 10 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude oily residue which was directly used in the next step.

To the crude residue from above step in EtOAc (1 mL) was added 10% Pd/C (10 mg) and the reaction was allowed to stir at rt under H_2 balloon pressure for 4 h until complete consumption of starting material was indicated by TLC analysis. The reaction mixture was worked up by filtering it through a short celite bed followed by washing of the celite bed with EtOAc (4 × 5 mL). The combined organic phase were evaporated under reduced pressure to arrive at a crude residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (19:1) as the eluent to access pure **29** (33 mg, 62% yield over 2 steps) as colorless oil. IR (neat): ν_{max} 2942, 2866, 1463, 1383, 1147, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.40 (dd, J_1 = 10 Hz, J_2 = 5 Hz, 1H), 3.82-3.76 (m, 2H), 3.65 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 3.33 (td, J_1 = 11 Hz, J_2 = 3 Hz, 1H), 2.22 – 2.13 (m, 1H), 2.09-1.99 (m, 1H), 1.80-1.77 (m, 2H), 1.65 (ddd, J_1 = 10 Hz, J_2 = 6 Hz, J_3 = 3 Hz, 1H), 1.54 – 1.46 (m, 1H), 1.41 – 1.29 (m, 1H), 1.08 (br s, 21H), 0.99 (d, J = 7 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.84, 67.31, 67.01, 43.82, 42.75, 38.38, 33.49, 29.90, 18.14 (3C), 18.09 (3C), 12.97, 12.40 (3C). HRMS (ESI) m/z calcd for $C_{18}H_{37}O_2Si$ $(M+H)^+$: 313.2557; found: 313.2558.

rel-(4aS,6S,7R,7aS)-7-methyloctahydrocyclopenta[c]pyran-6-ol (31): To a stirred solution of **30**[9] (250 mg, 1.05 mmol) in dry EtOAc (3 mL) was added 10% Pd/C (50 mg). The mixture was then allowed to stir at rt under H_2 balloon pressure for 3 h until complete consumption of starting material was indicated by TLC analysis. The reaction mixture was worked up by filtering it through a short celite bed followed by washing of the celite bed with EtOAc (4 × 5 mL). The combined organic phase were evaporated under reduced pressure to arrive at a crude residue directly used in the next step.

To the solution of crude residue resulting from the above step in 2.5 mL MeOH was added $NaBH_4$ (40 mg, 1.05 mmol) at 0 °C. The mixture was then allowed to stir at rt for 1 h until complete consumption of starting material was indicated by TLC analysis. The reaction mixture was quenched with H_2O followed by extraction with EtOAc (3 × 10 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (1: 1) as the eluent to access the pure alcohol **31** (136 mg, 83% yield over 2 steps) as colourless oil. IR (neat): ν_{max} 3442, 2924, 1455, 1210, 1108, 913, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 – 3.84 (m, 2H), 3.81 (dd, J_1 = 12, J_2 = 3 Hz, 1H), 3.63 (dd, J_1 = 12, J_2 = 4 Hz, 1H), 3.41 (td, J_1 = 11 Hz, J_2 = 3 Hz, 1H), 2.28 – 2.20 (m, 1H), 2.14-2.05 (m, 1H), 2.03-1.96 (m, 1H), 1.77 – 1.58 (m, 3H), 1.45-1.38 (m, 2H), 1.08 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.78, 67.14, 66.79, 45.10, 42.04, 40.00, 33.96, 29.88, 16.67. HRMS (ESI) m/z calcd for $C_9H_{17}O_2$ $(M+H)^+$: 157.1223; found: 157.1229.

rel-(4aS,6R,7R,7aS)-7-methyloctahydrocyclopenta[c]pyran-6-yl 4-nitrobenzoate (32): To an ice cold solution of DIAD (0.5 mL, 2.56 mmol, 4 equiv.) at 0 °C in dry THF (2 mL), PPh_3 (1.34 g, 5.12 mmol, 8 equiv.) was added and allowed to stir for 10 min., thereafter a solution of alcohol **31** (100 mg, 0.64 mmol) in dry THF (2 mL) was added at same temperature. Subsequently, after another 10 min. *p*-nitrobenzoic acid (2.13 g, 12.80 mmol,

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20 equiv.) was added and the mixture was allowed to warm to rt and continued stirring for another 8 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with EtOAc (3 × 15 mL). Drying of the organic phase over Na_2SO_4 and then solvent removal under reduced pressure gave a solid residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (8:2) as the eluent to access the *p*-nitrobenzoate derivative **32** (146 mg, 75% yield) as white solid. IR (neat): ν_{max} 2954, 1720, 1606, 1527, 1348, 1275, 1103, 937, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.0 Hz, 2H), 8.18 (d, *J* = 9.0 Hz, 2H), 5.56 (td, J_1 = 6 Hz , J_2 = 3 Hz, 1H), 3.90-3.85 (m, 2H), 3.71 (dd, J_1 = 12 Hz , J_2 = 4 Hz, 1H), 3.37 (td, J_1 = 12 Hz, J_2 = 2 Hz, 1H), 2.48 – 2.38 (m, 1H), 2.35 – 2.27 (m, 1H), 2.08 (ddd, J_1 = 15 Hz, J_2 = 7 Hz, J_3 = 3 Hz, 1H), 1.96 (ddd, J_1 = 15 Hz, J_2 = 8 Hz, J_3 = 3 Hz, 1H), 1.78 – 1.73 (m, 1H), 1.63 – 1.57 (m, 1H), 1.46 (dtd, J_1 = 14 Hz, J_2 = 11 Hz, J_3 = 4 Hz, 1H), 1.05 (d, *J* = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.23, 150.48, 136.08, 130.57 (2C), 123.54 (2C), 79.27, 67.15, 66.50, 44.32, 39.26, 36.62, 34.04, 29.75, 12.26. HRMS (ESI) m/z calcd for $C_{16}H_{20}NO_5$ $(M+H)^+$: 306.1336; found: 306.1342.

***rel-(4aS,6R,7R,7aS)-7-methyloctahydrocyclopenta[c]pyran-6-ol [Proposed structure of scholarein A] (9) via 29*:** To a stirred solution of **29** (33 mg, 0.11 mmol) in THF (1 mL), 10% HCl (1 mL) was added at rt and the reaction was allowed to stir for 12 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by quenching it with sat. aq. $NaHCO_3$ solution followed by extraction with EtOAc (3 × 10 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave an oily residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (7: 3) as the eluent to access the synthetic version of proposed scholarein A (13 mg, 80%) as colourless oil. IR (neat): ν_{max} 3454, 2928, 1275, 1260, 1107, 1039, 977 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29-4.25 (m, 1H), 3.85 – 3.80 (m, 2H), 3.68 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 3.33 (td, J_1 = 11 Hz, J_2 = 2 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.15 – 2.04 (m, 1H), 1.85 (ddd, J_1 = 14 Hz, J_2 = 6 Hz, J_3 = 3 Hz, 1H), 1.77 (ddd, J_1 = 14 Hz, J_2 = 8 Hz, J_3 = 3.0 Hz, 1H), 1.65 – 1.59 (m, 1H), 1.56 – 1.49 (m, 1H), 1.43 – 1.32 (m, 2H), 1.01 (d, *J* = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.65, 67.24, 66.86, 43.13, 41.54, 37.58, 33.83, 30.16, 11.70. HRMS (ESI) m/z calcd for $C_9H_{17}O_2$ $(M+H)^+$: 157.1223; found: 157.1227.

rel-(4aS,6R,7R,7aS)-7-methyloctahydrocyclopenta[c]pyran-6-ol [Proposed structure of scholarein A] (9) via 32: To a stirred solution of *p*-nitrobenzoate derivative **32** (100 mg, 0.33 mmol) in MeOH (2 mL) was added K_2CO_3 (228 mg, 1.65 mmol, 5 equiv.) and the mixture was allowed to stir at rt for 1 h until complete consumption of starting material was indicated by TLC analysis. The reaction was quenched with sat. aq. NH_4Cl solution followed by extraction with EtOAc (3 × 15 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave an oily residue which was subjected to SiO_2-gel column chromatography using hexanes/EtOAc (7: 3) as the eluent to access the synthetic version of proposed scholarein A (46 mg, 90%) as colourless oil. IR (neat): ν_{max} 3454, 2928, 1275, 1260, 1107, 1039, 977 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29-4.25 (m, 1H), 3.85 – 3.80 (m, 2H), 3.68 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 3.33 (td, J_1 = 11 Hz, J_2 = 2 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.15 – 2.04 (m, 1H), 1.85 (ddd, J_1 = 14 Hz, J_2 = 6 Hz, J_3 = 3 Hz, 1H), 1.77 (ddd, J_1 = 14 Hz, J_2 = 8 Hz, J_3 = 3.0 Hz, 1H), 1.65 – 1.59 (m, 1H), 1.56 – 1.49 (m, 1H), 1.43 – 1.32 (m, 2H), 1.01 (d, *J* = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.65, 67.24, 66.86, 43.13, 41.54, 37.58, 33.83, 30.16, 11.70. HRMS (ESI) m/z calcd for $C_9H_{17}O_2$ $(M+H)^+$: 157.1223; found: 157.1227.

Conflicts of interest

There are no conflicts to declare.

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Total Syntheses of several Iridolactones and the Putative Structure of Noriridoid Scholarein A: An Intramolecular Pauson-Khand Reaction based One-stop Synthetic Solution

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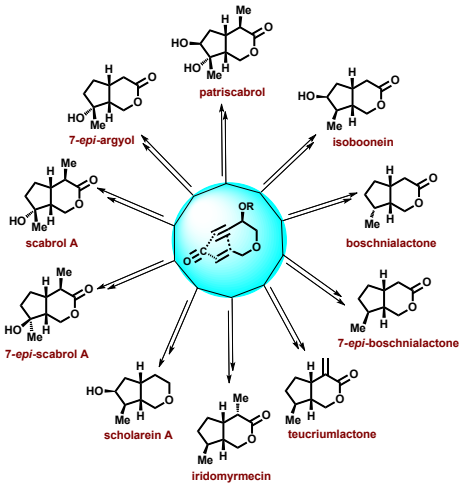

A general synthetic strategy featuring a diastereoslective intramolecular Pauson-Khand reaction (IPKR) to construct the iridoid framework followed by some strategic synthetic manipulations to access ten iridoids in a stereocontrolled manner is delineated.