Enantiospecific Total Syntheses and Assignment of Absolute Configuration of Cannabinol-Skeletal Carbazole Alkaloids Murrayamines-O and -P

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Enantiospecific Total Syntheses and Assignment of Absolute Configuration of Cannabinol-Skeletal Carbazole Alkaloids Murrayamines-O and -P

Dattatraya H. Dethe,* Saikat Das, Balu D. Dherange, and Samarpita Mahapatra[a]

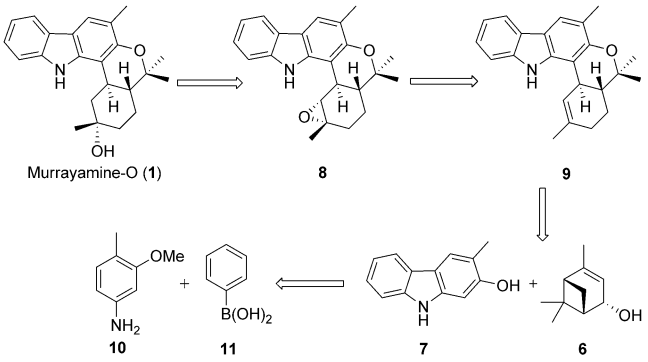
Dedicated to Dr. A. V. Rama Rao on the occasion of his 80th birthday

Abstract: First enantiospecific total syntheses of the cannabinol-skeletal carbazole alkaloids murrayamines-O and -P isolated from root barks of *Murraya euchrestifoli*, have been accomplished by highly diastereoselective, Lewis acid catalyzed coupling reactions of commercially available monoterpenes with carbazole derivative, which in addition to confirming the structure also established the absolute configuration of the natural products. Synthesis of both natural products and their enantiomers was achieved with high atom economy, in a protecting-group free manner and in six steps longest linear sequence from commercially available aniline derivative and verbenol.

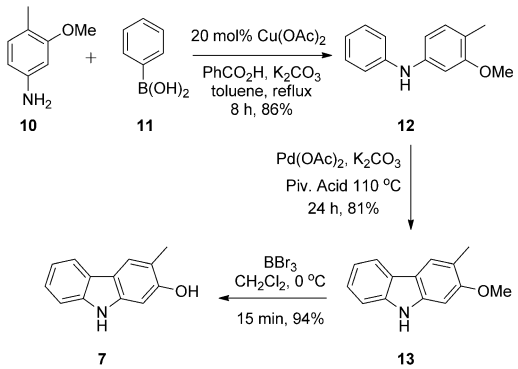
Murrayamines-O (**1**) and -P (**2**) are the two novel pentacyclic alkaloids isolated from the plant of genus *Murraya*.[1] Both **1** and **2** are the first representatives of cannabinol-skeletal carbazole alkaloids. *Murraya* is a genus of flowering plants in the citrus family *Rutaceae*, that has been used in traditional medicine for the treatment of fever, pain, diabetics, dysentery, painful inflammatory conditions, to induce labor and for cancer treatments.[2] Murrayamine and related carbazole alkaloids have been reported to show a potent antiplatelet aggregation activity.[3] The structure of **1** and **2** were determined by extensive 1D and 2D NMR analysis. The relative stereochemistry was assigned based on splitting patterns; coupling constants and NOESY experiments revealed a *trans* fused chair-like oxadecalin core and the equatorial C-3 methyl.

So far more than fifty natural products belonging to this family and having various potent biological activities have been isolated.[4] Although there have been no synthesis reported of murrayamine-O/P, recently racemic total synthesis of some natural products of this class such as murrayazoline (**3**),[5,6] cyclomahanimbine (**4**),[6] murrafoline-A (**5**),[7] and related natural products[8] have been reported in the literature. Also, there are few reports on enantioselective synthesis of these natural products either by chiral pool or asymmetric catalytic synthesis.[9] With our ongoing interest in total synthesis[10–12] of biologically active natural products,[13,14] herein we report the first enantiospecific total syntheses of murrayamine-O (**1**) and murrayamine-P (**2**) as well as their antipodes *ent*-**1** and *ent*-**2**, respectively, facilitated by Lewis acid catalyzed coupling of cyclic allylic alcohol **6** with carbazole derivative **7** for one pot C–C and C–O bond formation and a strategic effort to avoid the use of protecting group and expensive reagents.

It was envisioned that murrayamine-O/P could be obtained from compound **8** by regioselective epoxide ring opening. Epoxide **8** could be easily accessed from compound **9** by diastereoselective epoxidation. The key intermediate **9** in turn could be obtained by treatment of carbazole derivative **7** with verbe-



Scheme 1. Retrosynthetic analysis of murrayamine-O (**1**).



Scheme 2. Synthesis of carbazole derivative **7**.

[a] *Dr. D. H. Dethe, S. Das,[+] B. D. Dherange,[+] S. Mahapatra*
Department of Chemistry
Indian Institute of Technology Kanpur, Kanpur 208016 (India)
E-mail: ddethe@iitk.ac.in

[+] *These authors contributed equally to this work.*

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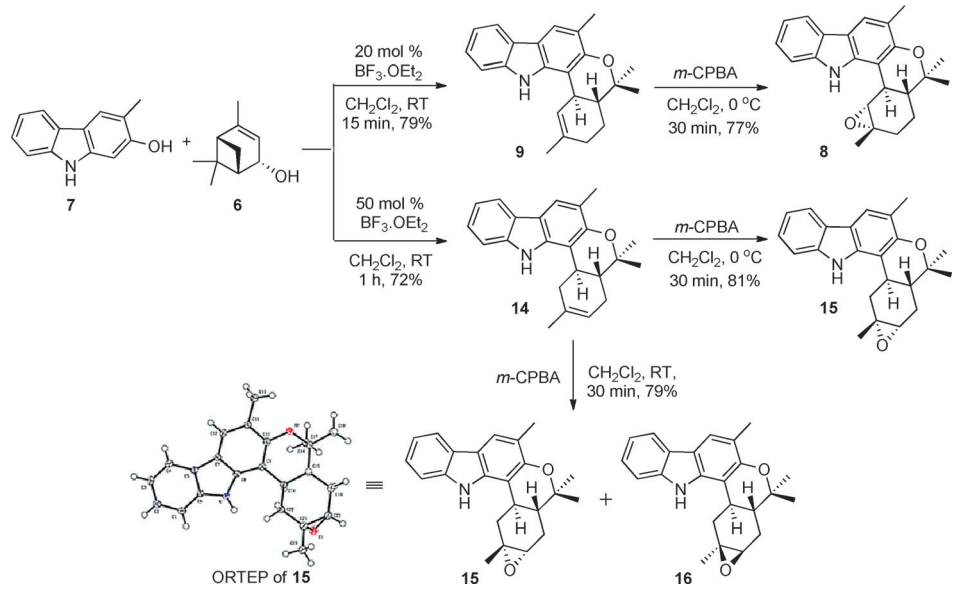


Scheme 3. Synthesis of pentacyclic core of murrayamine-O/P.

nol **6** by simultaneous C–C and C–O bond formation by taking advantage of the strained four-membered ring in verbenol **6** (Scheme 1).

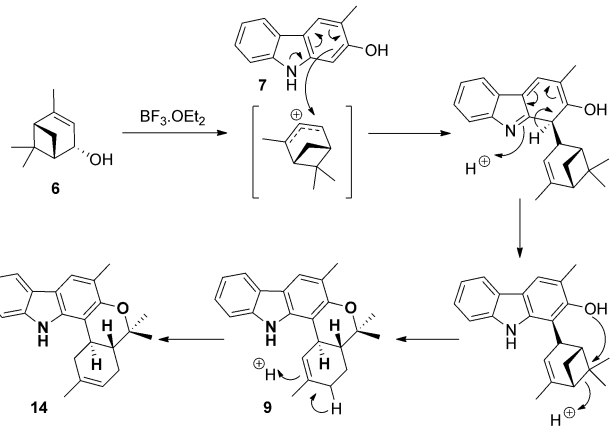
Carbazole derivative **7** could be synthesized using metal-catalyzed coupling reactions from aniline derivative **10** and phenyl boronic acid **11**. So to begin with, carbazole derivative **7** was prepared using three steps. A mixture of phenyl boronic acid **11** and compound **10** on treatment with catalytic amount of copper acetate in refluxing toluene under basic conditions afforded compound **12** in 86% yield (Scheme 2).[15]

Compound **12**, on treatment with catalytic amount of $Pd(OAc)_2$ furnished **13** in 81% yield.[6] Demethylation of **13** by BBr_3 at 0 °C afforded the required carbazole **7**. Carbazole **7** and (−)-(*S*)-*cis*-verbenol (**6**) were then merged together using 20 mol% $BF_3{\cdot}OEt_2$ catalyzed coupling reaction to furnish the pentacyclic core **9** of murrayamines-O (**1**) and -P (**2**) as a single diastereomer in 79% isolated yield in just 15 min at room temperature (Scheme 3).

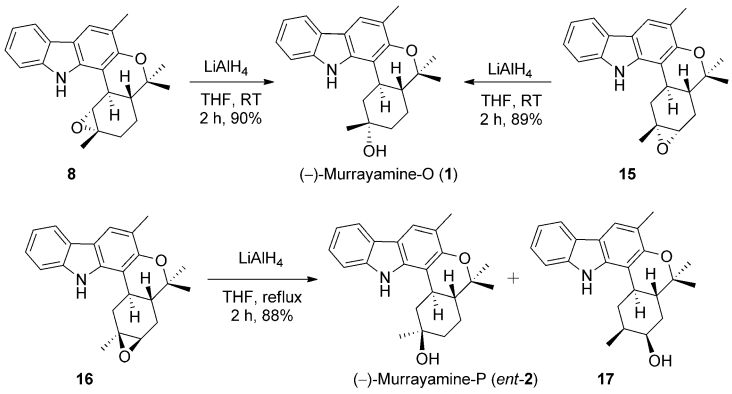
Formation of the single diastereomer might be due to the favorable *exo* approach of incoming carbazole derivative on allylic carbocation, as *endo* attack is sterically hindered, as shown in Scheme 4. When the reaction was allowed to stir for 1 h, isomerization of the double bond was observed to generate compound **14**, presumably due to the thermodynamic stability of the latter.

It was contemplated that individual epoxidation of compound **9** and **14**, followed by regioselective opening of epoxides thus formed would generate both natural products murrayamines-O (**1**) and -P (**2**). To our delight independent epoxidation of compound **9** and **14** with *m*-CPBA at 0 °C afforded epoxides **8** and **15** as single diastereomers in 77 and 81% yield, respectively. Stereochemistry of epoxide **15** was established by single crystal X-ray analysis.[16] Interestingly when epoxidation of compound **14** was carried out at room temperature, a diastereomeric mixture of epoxides **15** and **16** were obtained in 12:1 ratio with 79% yield. Regioselective independent opening of the epoxides **8** and **15** by lithium aluminum hydride (LAH) furnished **1** as a single diastereomer in 90 and 89% yield (Scheme 5), the NMR spectroscopic data for which (^1H, ^{13}C, IR, HRMS) were identical to those reported for the natural product.[1]

The optical rotation data obtained for **1** $[\alpha]_D = -117$ (*c* 0.07, $CHCl_3$) also confirmed that the absolute configuration (1′*R*,3′*R*,6′*R*) depicted in Figure 1



Scheme 4. Plausible mechanism for formation of pentacyclic core **14** from carabzole **7** and verbenol **6**.



Scheme 5. Completion of total synthesis of murrayamines-O and -P.

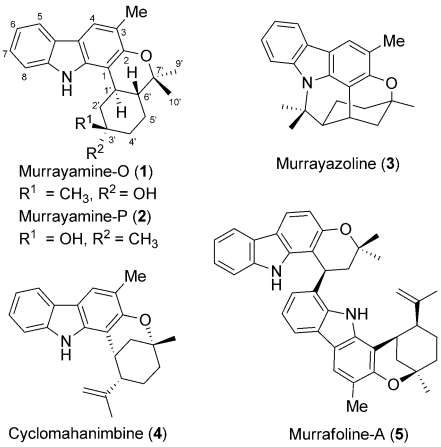
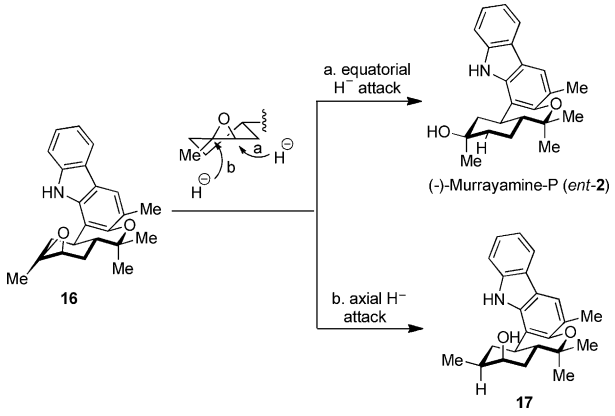


Figure 1. Selected examples of natural products from plant genus *Murraya*.

corresponds to that of the natural product (−)-murrayamine-O ($[\alpha]_D = -137.6$ (*c* 0.07, $CHCl_3$)).[1]

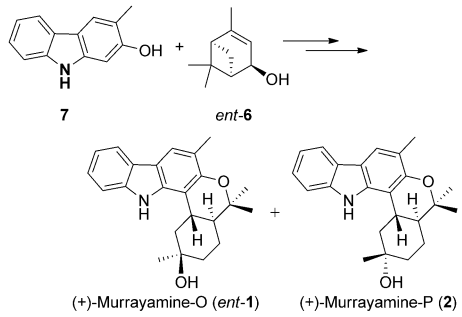
Surprisingly, minor epoxide **16**, on treatment with LAH resulted in formation of antipode of murrayamine-P (*ent*-**2**) along with secondary alcohol **17** in 2:3 ratio with 88% yield. Although spectral data of synthetic **2** (^1H, ^{13}C, IR, HRMS) were in complete agreement with natural murrayamine-P, the optical rotation sign of synthetic **2** ($[\alpha]_D = -89.8$ (*c* 0.1, $CHCl_3$)) was exactly opposite to that of natural murrayamine-P ($[\alpha]_D = +92$ (*c* 0.015, $CHCl_3$)),[1] confirming that synthetic **2** is an antipode of the natural murrayamine-P.[1] Poor regioselectivity observed in opening of epoxide **16** might be due to preference for axial hydride attack by LAH on cyclohexane epoxide (Scheme 6).



Scheme 6. Mechanism of epoxide **16** opening by LAH.

Natural (+)-murrayamine-P (**2**) and antipode of (−)-murrayamine-O (**1**) were synthesized starting from (+)-(*R*)-*cis*-verbenol (*ent*-**6**) in a similar fashion with 1.37 and 30.63% overall yield, respectively (Scheme 7). Optical rotation $[\alpha]_D = +91.2$ (*c* 0.1, $CHCl_3$) for synthetic murrayamine-P (**2**) established its absolute configuration as (1′*S*,3′*S*,6′*S*).

We also became interested in coupling of carbazole derivative **7** with cyclic alcohol **18** and its enantiomer (*ent*-**18**). Thus, carbazole **7** and alcohol **18**, on treatment with 10 mol% $BF_3{\cdot}OEt_2$, gave pentacyclic core **9** in 74% yield in 20 min. When the reaction was quenched within 5 min, we were able to isolate compound **19** in 80% yield as a single diastereomer. The structure and stereochemistry of **19** was established by single crystal X-ray analysis (Figure 2).[16]



Scheme 7. Total syntheses of (+)-murrayamines-O (*ent*-**1**) and (+)-murrayamine-P (**2**).

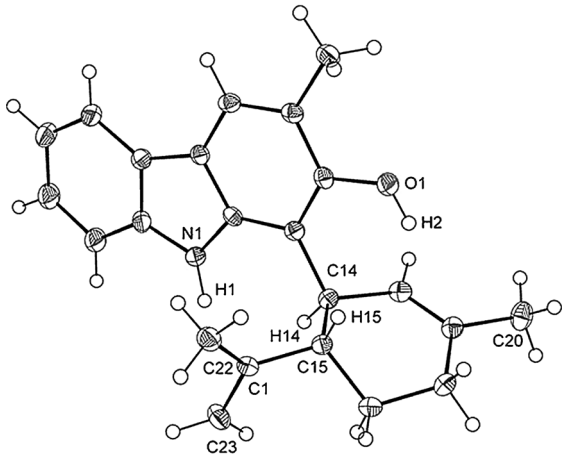
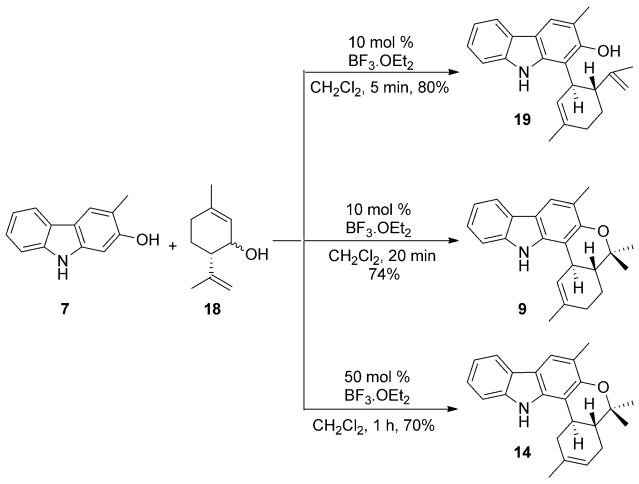


Figure 2. ORTEP diagram of ent-**19**. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 8. Synthesis of pentacyclic core of murrayamine from monoterpene **18**.

Interestingly, when 50 mol% of $BF_3{\cdot}OEt_2$ was used and the reaction was allowed to continue for 1 h we also observed formation of isomerization compound **14** as in the case of verbenol **6** in 70% yield (Scheme 8). Synthesis of compound **9** and **14** also constitutes formal syntheses of murrayamines-O (**1**) and P (**2**).

In conclusion, using a simple strategy we have achieved first enantiospecific total syntheses of representatives of cannabinol-skeletal carbazole alkaloids murrayamine-O and -P. Synthesis of both natural products and their enantiomers were achieved in highly atom economical, gram scale, protecting-group free manner, in six steps longest linear sequence starting from (−)-(*S*)- and (+)-(*R*)-*cis*-verbenol.

Experimental Section

Full details of experimental procedures, characterization data, and NMR spectra can be found in the Supporting Information.

Acknowledgements

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Keywords: cannabinol carbazole alkaloids · murrayamines · natural products · total synthesis · verbenol

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[16] CCDC 1034660 ((−)-**15**) and CCDC 1017679 ((+)-1**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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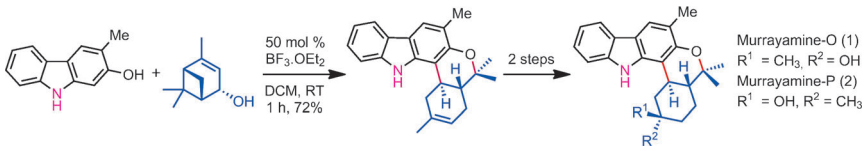

Back to the roots: First enantiospecific total syntheses of the cannabinol-skeletal carbazole alkaloids murrayamines-O and -P isolated from root barks of *Murraya euchrestifoli*, have been accomplished by highly diastereoselective, Lewis acid catalyzed coupling reactions of commercially available monoterpenes with carbazole derivative (see scheme).

Total Synthesis

D. H. Dethe, S. Das, B. D. Dherange, S. Mahapatra*

■■ – ■■

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