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Synthesis of Prenyl- and Geranyl-Substituted Carbazole Alkaloids by DIBAL-H Promoted Reductive Pyran Ring Opening of Dialkylpyrano[3,2-*a*]carbazoles**

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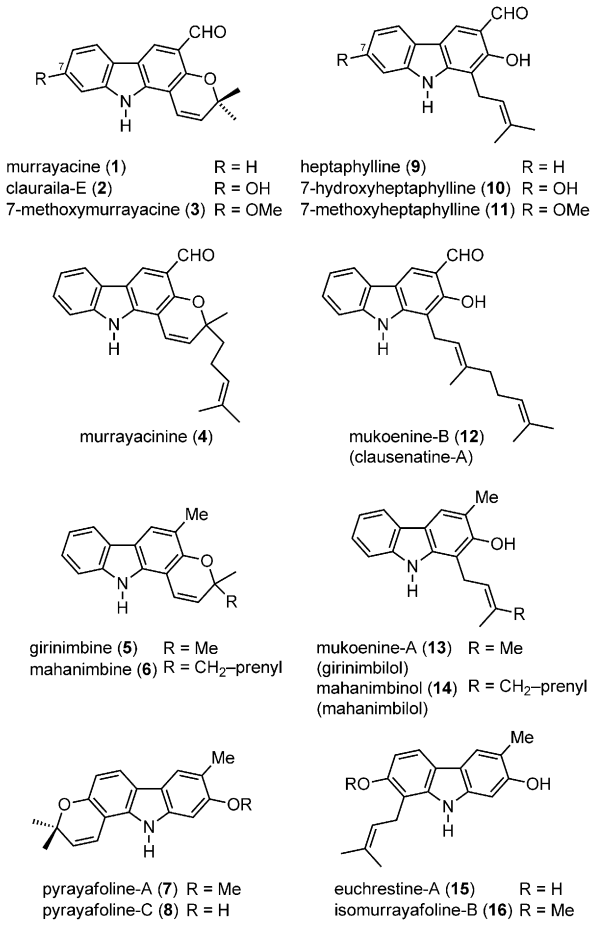
Abstract: The DIBAL-H promoted reductive pyran ring opening of dialkylpyrano[3,2-*a*]carbazoles provides a direct access to a broad range of prenyl- and geranyl-substituted carbazoles. Formation of a pyran ring followed by reductive ring opening represents a new method for the introduction of prenyl and geranyl groups. In the course of the present work, we achieved the first total syntheses of the following eight carbazole alkaloids: clauraila-E, 7-hydroxyheptaphylline, 7-methoxyheptaphylline, mukoenine-B (clausenatine-A), mukoenine-A (girinimbilol), mahanimbinol (mahanimbilol), euchrestine-A, and isomurrayafoline-B.

Carbazole alkaloids show a broad structural variety and are important because of their pharmacological potential. Two groups of carbazoles that have attracted a lot of interest recently are the pyrano[3,2-*a*]carbazoles (e.g., compounds **1**–**8**, Scheme 1) and the prenyl- or geranyl-substituted carbazole alkaloids (e.g., compounds **9**–**16**).[1,2] A broad range of carbazoles belonging to these two classes has been isolated by the groups of Furukawa, Ito, Wu, and others from plants of the genera *Murraya* and *Clausena* (family: Rutaceae).[1] Diverse synthetic routes to pyrano[3,2-*a*]carbazoles using different modes for annulation of the pyran ring have been described.[3–5] On the other hand, many procedures have been developed for the selective introduction of prenyl groups by coupling reactions using transition metals.[6–10] Recently, we have reported a method for specific prenylation by palladium(0)-catalyzed Stille or Suzuki–Miyaura coupling of bromocarbazoles with the corresponding *tert*-prenyl metal species.[10] However, the palladium(0)-catalyzed cross coupling requires an appropriately halogenated carbazole as precursor. For the biosynthesis of the carbazole alkaloids **1**–**16** in terrestrial plants, 2-hydroxy-3-methylcarbazole represents the parent compound.[2] Prenylation or geranylation of 2-hydroxy-3-methylcarbazole and possibly further oxidation or oxygenation biogenetically leads to the prenyl- and geranyl-substituted carbazole alkaloids **9**–**16**. The *gem*-dialkyl-substituted pyrano[3,2-*a*]carbazoles **1**–**8** have been suggested to derive from cyclization of the corresponding prenyl- and geranyl-substituted carbazoles **9**–**16**.[2] Herein, we describe an efficient access to prenyl- and geranyl-substituted hydroxycarbazoles by virtual reversal of the biogenetic sequence. In our synthetic approach, the annulation of the pyran ring at a 2-hydroxycarbazole is followed by a DIBAL-H



Scheme 1. Structures of the naturally occurring pyrano[3,2-*a*]carbazole alkaloids **1**–**8** and the corresponding prenyl- and geranyl-substituted tricyclic carbazole alkaloids **9**–**16**.

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[**] *Part 120 of "Transition Metals in Organic Synthesis". For part 119, see: C. Schuster, C. Börger, K. K. Julich-Gruner, R. Hesse, A. Jäger, G. Kaufmann, A. W. Schmidt, H.-J. Knölker,* Eur. J. Org. Chem. ***2014***, *DOI: 10.1002/ejoc.201402495. DIBAL-H = diisobutylaluminum hydride.*

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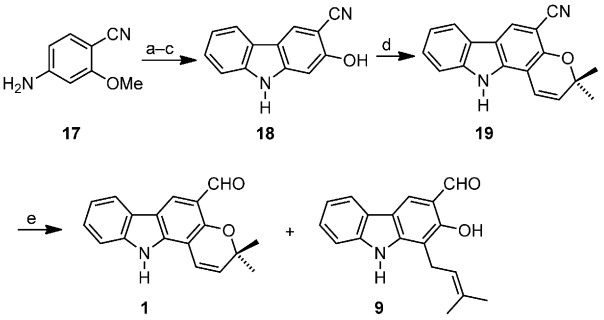
promoted reductive opening of the pyran ring, which leads to the corresponding prenyl- or geranyl-substituted hydroxycarbazoles, respectively. The prerequisite 2-hydroxycarbazoles are readily available using our palladium-catalyzed construction of the carbazole framework.[2]

For our approach to murrayacine (**1**) and heptaphylline (**9**),[11] we used the arylamine **17** as starting material (Scheme 2). We had already demonstrated that the cyano



Scheme 2. Synthesis of murrayacine (**1**) and heptaphylline (**9**): a) 1.2 equiv **17**, 1.0 equiv PhI, 5 mol% $Pd(OAc)_2$, 10 mol% SPhos, 1.4 equiv Cs_2CO_3, toluene, 100 °C, 29 h (99%); b) 21 mol% $Pd(OAc)_2$, 21 mol% $Cu(OAc)_2$, 25 mol% K_2CO_3, HOPiv, air, 100 °C, 15.5 h (74%); c) 25 equiv pyridine-HCl, 155 °C (MW), 45 min (96%); d) 1. 1.5 equiv methyl 2-methylbut-3-yn-2-yl carbonate, 1.3 equiv DBU, 2.1 mol% CuI, MeCN, RT, 25.5 h, 2. toluene, reflux, 25 h (85%, two steps); e) 3.0 equiv DIBAL-H, CH_2Cl_2, −78 to −30 °C, 3.5 h (21% **1**, 75% **9**).

group is compatible with our palladium-catalyzed approach and serves as surrogate for a formyl substituent.[12] Thus, Buchwald–Hartwig coupling[13] of the arylamine **17** and iodobenzene followed by palladium(II)-catalyzed oxidative cyclization[14] and cleavage of the methyl ether afforded the 2-hydroxycarbazole **18**. Formation of the corresponding dimethylpropargyl ether using Godfrey's method[15] followed by thermally induced rearrangement led to the pyrano[3,2-*a*]carbazole **19**. Treatment of compound **19** with 2.5 equiv DIBAL-H at −78 °C afforded murrayacine (**1**) in 80% yield by reduction of the cyano group (Table 1).[16] Interestingly, from this reaction we isolated heptaphylline (**9**) as a by-product (16% yield),[17] which obviously resulted from a concomitant DIBAL-H promoted reductive opening of the pyran ring. An optimization towards the formation of heptaphylline (**9**) was achieved by using slightly more DIBAL-H (3.0 equiv) and an increase of the temperature to −30 °C after addition of the reducing agent. These reaction conditions provided heptaphylline (**9**) in 75% yield along with 21% of murrayacine (**1**). The structures of heptaphylline (**9**) and murrayacine (**1**) were additionally confirmed by X-ray crystal structure determinations (Figure 1 and Supporting Information).[18]

Table 1. Reaction conditions for the DIBAL-H promoted reductive ring opening of the pyrano[3,2-*a*]carbazole **19** to heptaphylline (**9**).

Reaction conditions	Yield [%] **1**	**9**
2.5 equiv DIBAL-H, CH_2Cl_2, −78 °C, 3.5 h	80	16
3.0 equiv DIBAL-H, CH_2Cl_2, −78 to −30 °C, 3.5 h	21	75

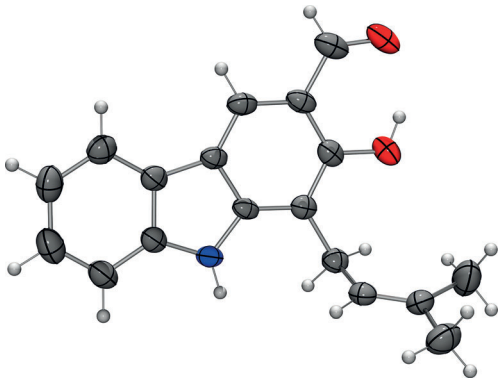
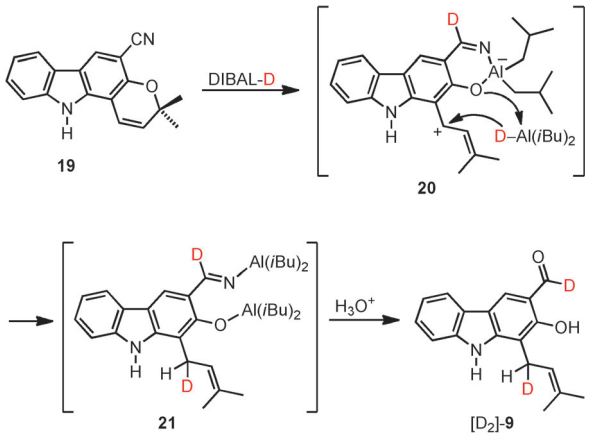
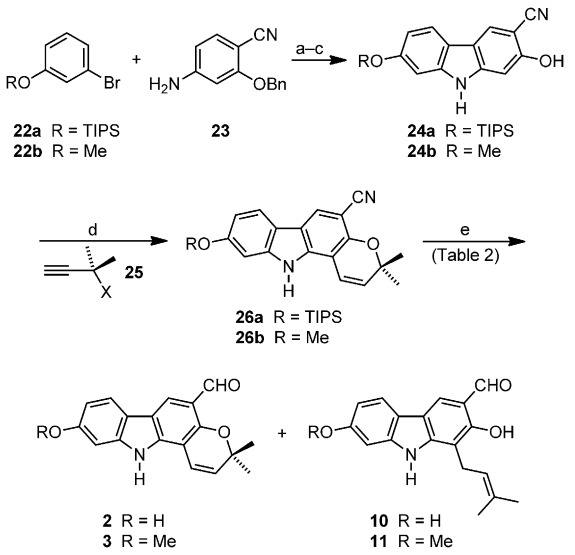


Figure 1. Molecular structure of heptaphylline (**9**) in the crystal (ORTEP plot showing thermal ellipsoids at the 50% probability level).

We propose the following mechanism for the DIBAL-H promoted reductive ring opening of the pyran ring, which has been supported by an experiment using freshly prepared diisobutylaluminum deuteride (DIBAL-D) as reducing agent (Scheme 3).[19] DIBAL-H is well-known as a Lewis acidic reducing agent.[20] Thus, the initial reduction of the cyano group generates a Lewis acid complex with the aluminum coordinated to both, the imine nitrogen atom and the oxygen atom of the pyran ring. The resulting Lewis acid promoted opening of the pyran ring to intermediate **20** opens up the way for reduction by a second equivalent of reducing agent, which proceeds by attack of hydride (deuteride) at the benzylic position. Hydrolytic workup of the final Lewis acid complex **21** leads to the product. In agreement with this proposal, the reduction of **19** with DIBAL-D provided the double deuterated heptaphylline $[D_2]$-**9** (MS: $[M^+]=281$) with a deuterium incorporation of about 100% at the formyl group and 90–95% at the benzylic position (see the Supporting Information).



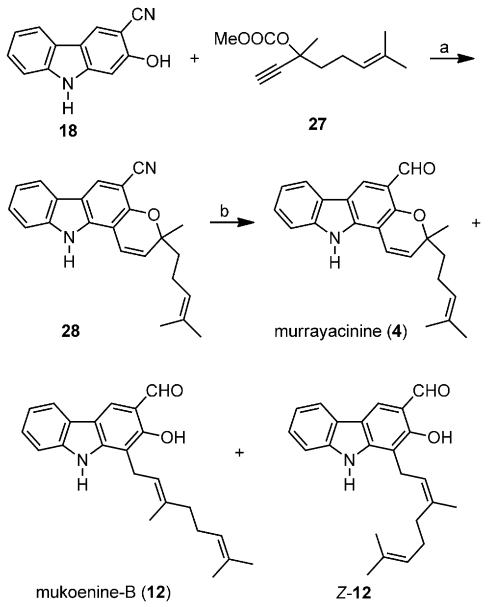
Scheme 3. Proposed mechanism for the reductive cleavage of the pyran ring supported by an experiment using DIBAL-D as reducing agent.



Scheme 4. Synthesis of **2**, **3**, **10**, and **11**: a) 1.2–1.3 equiv **23**, 1.0 equiv **22**, 5–6 mol% $Pd(OAc)_2$, 11–14 mol% SPhos, 1.4–1.7 equiv Cs_2CO_3, toluene, 100 °C, 21–31 h (96–100%); b) 20 mol% $Pd(OAc)_2$, 2.5 equiv $Cu(OAc)_2$, HOPiv, air, 130 °C (MW), 2–3 h (51–76%); c) **a**: 10% Pd/C, H_2, CH_2Cl_2/MeOH (1:1), RT, 25 h (86%); **b**: 4 equiv $AlCl_3$, dioxane, reflux, 2 h (69%); d) **a**: 1. 1.25 equiv **25a** (X = OH), 1.15 equiv TFAA, 2.8 equiv DBU, 0.5 mol% $CuCl_2$, MeCN, −20 to +15 °C, 8 h, 2. xylene, reflux, 23 h (72%, two steps); **b**: 1. 1.6 equiv **25b** (X = OCOOMe), 1.3 equiv DBU, 1.1 mol% CuI, MeCN, RT, 22 h, 2. toluene, reflux, 24 h (76%, two steps); e) Table 2.

The synthesis of the 7-oxygenated carbazoles **2**, **3**, **10**, and **11** started with a Buchwald–Hartwig coupling of the bromoarenes **22a** and **22b** with the arylamine **23** (Scheme 4). Subsequent palladium(II)-catalyzed oxidative cyclization and removal of the benzyl group provided the 2-hydroxycarbazoles **24**. Annulation of the pyran ring via Godfrey's procedure[15] afforded the pyrano[3,2-*a*]carbazoles **26**. Reduction of **26a** using DIBAL-H at −78 °C followed by removal of the silyl group with TBAF provided clauraila-E (**2**) in 86% yield (Table 2),[21] whereas addition of DIBAL-H at −78 °C followed by an increase of the temperature to −20 °C and desilylation led primarily to reductive pyran ring opening and afforded 7-hydroxyheptaphylline (**10**) in 71% yield (Table 2).[22] Along the same lines, DIBAL-H reduction of **26b** at −78 °C led to 7-methoxymurrayacine (**3**) in 68% yield,[23] whereas addition of DIBAL-H to **26b** at −78 °C and subsequent temperature increase to −40 °C afforded 7-methoxyheptaphylline (**11**) in 63% yield.[24]

We next investigated whether our procedure of reductive pyran ring opening could be applied to the conversion of homoprenyl-substituted pyrano[3,2-*a*]carbazoles to 1-geranyl-2-hydroxycarbazoles. Therefore, reaction of the 2-hydroxycarbazole **18** with carbonate **27**[25] was used to prepare the corresponding pyrano[3,2-*a*]carbazole **28** (Scheme 5 and Table 3). Reduction of compound **28** using DIBAL-H at −78 °C provided murrayacinine (**4**) in 87% yield (Table 3).[26] Addition of DIBAL-H at −78 °C followed by an increase of the temperature to −30 °C afforded a mixture of mukoenine-B (clausenatine-A) (**12**)[27] and its corresponding *Z*-isomer *Z*-**12** (ratio = 1:2.4) in 71% yield. Both compounds could be separated by HPLC (see the Supporting Information).



Scheme 5. Synthesis of murrayacinine (**4**) and mukoenine-B (**12**): a) 1. 1.0 equiv **18**, 1.5 equiv **27**, 1.3 equiv DBU, 0.7 mol% CuI, MeCN, RT, 15 h, 2. toluene, reflux, 24.5 h (82%); b) see Table 3.

Table 2. DIBAL-H promoted reductive ring opening of **26a** and **26b**.

	DIBAL-H	Reaction conditions	Products, Yields [%]
a	2.5 equiv	CH_2Cl_2, −78 °C, 3 h;[a]	**2** 86; **10** 14
a	3.0 equiv	CH_2Cl_2, −78 to −20 °C, 4.5 h;[a]	**2** 20; **10** 71
b	3.0 equiv	CH_2Cl_2, −78 °C, 3.5 h	**3** 68; **11** 9
b	3.0 equiv	CH_2Cl_2, −78 to −40 °C, 3 h	**3** 13; **11** 63

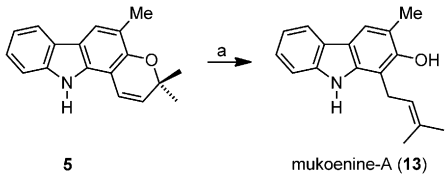
[a] then, 1.5 equiv TBAF, DMF, −20 °C to RT, 5 min.

Table 3. DIBAL-H promoted reductive ring opening of compound **28**.

Reaction conditions	Yield [%] **4**	**12** (*E*/*Z*)
3.5 equiv DIBAL-H, CH_2Cl_2, −78 °C, 3.5 h	87	–
4.0 equiv DIBAL-H, CH_2Cl_2, −78 to −30 °C, 5.5 h	16	71 (1:2.4)

According to our proposed mechanism (Scheme 3), a coordination of the aluminum center to the imine nitrogen atom and to the pyran oxygen atom is required to induce the pyran ring opening at the stage of intermediate **20** prior to reduction by the second equivalent of DIBAL-H. Thus, our DIBAL-H promoted reductive pyran ring opening should not be applicable to 3-methyl-substituted pyrano[3,2-*a*]carbazoles. In fact, treatment of girinimbine (**5**)[28] with four equivalents of DIBAL-H resulted in complete recovery of the starting material. Therefore, we envisaged to promote an opening of the pyran ring by the presence of an additional Lewis acid along with DIBAL-H. Addition of weak Lewis acids (1 equiv of magnesium bromide or tetrapropoxytitanium) along with an excess of DIBAL-H had no

effect and **5** could be re-isolated completely. However, addition of boron trichloride to a solution of girinimbine (**5**) at −78 °C followed by addition of DIBAL-H resulted in a pyran ring opening and afforded mukoenine-A (girinimbilol) (**13**) in 39% yield (Scheme 6, Table 4). The addition of aluminum Lewis acids (aluminum trichloride or ethylaluminum dichloride) along with the excess of DIBAL-H gave similar yields of **13**. Finally, an optimization was achieved by treatment of girinimbine (**5**) with an excess of tetrachlorosilane prior to addition of an excess of DIBAL-H at −78 °C and subsequent warming to room temperature. This procedure provided mukoenine-A (girinimbilol) (**13**) in 66% yield.[29] The structure of **13** was confirmed by an X-ray crystal structure determination (Figure 2).[30]



Scheme 6. Synthesis of mukoenine-A (**13**): a) 4 equiv DIBAL-H, 3 equiv $SiCl_4$, CH_2Cl_2, −78 °C to RT, 22 h (66%).

Table 4. DIBAL-H/Lewis acid promoted reductive pyran ring opening of girinimbine (**5**).

DIBAL-H	Lewis acid	Reaction time[a]	**13**, Yield [%]
3.0 equiv	1.0 equiv BCl_3	3 h	39
2.0 equiv	1.0 equiv $AlCl_3$	2 h	39
2.5 equiv	1.0 equiv $EtAlCl_2$	2.5 h	32
4.0 equiv	3.0 equiv $SiCl_4$	22 h	66

[a] Reaction conditions: CH_2Cl_2, −78 °C to RT.

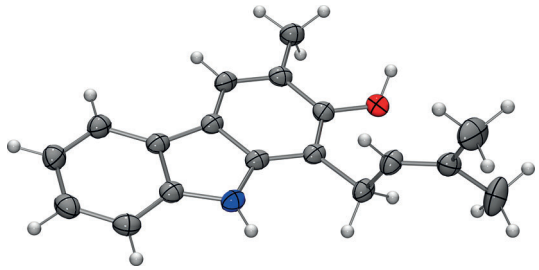
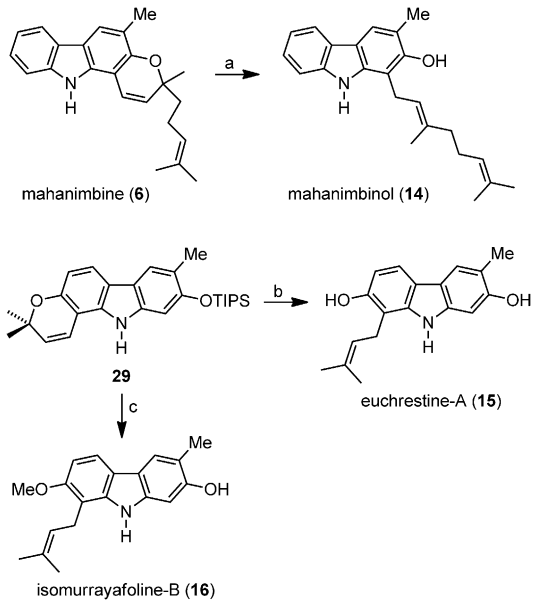


Figure 2. Molecular structure of mukoenine-A (**13**) in the crystal (ORTEP plot showing thermal ellipsoids at the 50% probability level).

Reductive pyran ring opening of mahanimbine (**6**)[31] with an excess of DIBAL-H and tetrachlorosilane using the conditions optimized above for the reaction of **5** afforded mahanimbinol (mahanimbilol) (**14**)[32] in 33% yield as single isomer (Scheme 7). Finally, we have studied the reductive pyran ring opening of compound **29**, which served as precursor for our recent total synthesis of pyrayafoline-A (**7**) and pyrayafoline-C (**8**).[4d] Following further fine-tuning of the reaction conditions,



Scheme 7. Synthesis of mahanimbinol (**14**), euchrestine-A (**15**), and isomurrayafoline-B (**16**): a) 4 equiv DIBAL-H, 4 equiv $SiCl_4$, CH_2Cl_2, −78 °C to RT, 18 h (33%); b) 1. 3 equiv DIBAL-H, 2 equiv $SiCl_4$, toluene, −78 °C to 10 °C, 1.75 h, 2. 1.5 equiv TBAF, DMF, −15 °C to RT, 10 min (93%, two steps); c) 1. 3 equiv DIBAL-H, 2 equiv $SiCl_4$, toluene, −78 °C to 10 °C, 1.75 h, 2. 1.3 equiv NaH, 1.5 equiv Me_2SO_4, THF, 0 °C to RT, 13 h, 3. 1.5 equiv TBAF, DMF, −15 °C to RT, 10 min (55%, three steps).

reduction of **29** with DIBAL-H in the presence of tetrachlorosilane and subsequent removal of the silyl group provided euchrestine-A (**15**)[33] in 93% yield. This result emphasizes that by individual optimization of the reaction conditions for the reductive pyran ring opening, excellent yields are feasible for the resulting prenylcarbazoles. Finally, reductive pyran ring opening of **29** followed by first methylation and then desilylation led to isomurrayafoline-B (**16**).[34] The structure of compound **16** was additionally confirmed by an X-ray analysis (Figure 3).[35]

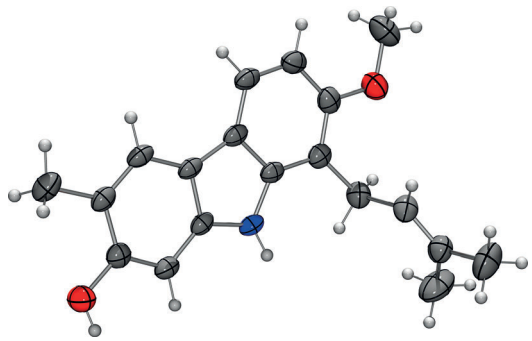


Figure 3. Molecular structure of isomurrayafoline-B (**16**) in the crystal (ORTEP plot showing thermal ellipsoids at the 50% probability level).

In conclusion, in the present work we have reported highly efficient routes to the pyrano[3,2-*a*]carbazole alkaloids murrayacine (**1**), clauraila-E (**2**), 7-methoxymurrayacine (**3**), and murrayacinine (**4**) using a cyano group as surrogate for the

formyl substituent. Most noteworthy, we have developed a DIBAL-H promoted reductive pyran ring opening of appropriate dialkylpyrano[3,2-*a*]carbazoles which provides an easy access to the corresponding prenyl- and geranyl-substituted carbazole alkaloids **9**–**16**. For eight carbazole alkaloids we have described the first total synthesis: clauraila-E (**2**), 7-hydroxyheptaphylline (**10**), 7-methoxyheptaphylline (**11**), mukoenine-B (clausenatine-A) (**12**), mukoenine-A (girinimbilol) (**13**), mahanimbinol (mahanimbilol) (**14**), euchrestine-A (**15**), and isomurrayafoline-B (**16**). The spectroscopic data for our synthetic compounds **1**–**4** and **9**–**16** are in full agreement with those reported for the natural products and thus confirm the previous structural assignments. A study of the pharmacological activities of the carbazole alkaloids described herein is ongoing. We anticipate that the scope of our DIBAL-H promoted reductive pyran ring opening is much broader than shown herein as this transformation may be applicable to a broad range of 2,2-dialkyl-2*H*-chromene derivatives. The sequence of pyran ring formation followed by reductive ring opening may be applied as a new method for the introduction of prenyl groups.

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Keywords: alkaloids · C–H bond activation · natural products · palladium · reduction

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pendent: 2479 (R_{int} = 0.0254), 197 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0328; wR_2 = 0.0731; maximal residual electron density: 0.125 e Å^{-3}. CCDC 1003544 contains the supplementary crystallographic data for this structure. 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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