A rapid entry to *C*-prenylcarbazoles: total synthesis of clausamine C–D, clausevatine D and clausine F†

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The key prenylcarbazole precursor 33 was readily assembled from diester 30 by an ester-driven *para*-Claisen rearrangement followed by selective removal of the ester function. Unusual oxidative cyclization of 33 by *m*-CPBA resulted in the total synthesis of tetracyclic carbazole natural products 3 and 11.

The carbazole alkaloids are a well-known class of secondary metabolites of plant origin. They display a wide variety of biological activities, namely antitumor, antibacterial, anti-inflammatory and antifungal activities.[1] Moreover, carbazole nuclei are prevalent in various functional organic materials and potential medicinal agents.[2,3] Consequently, a large number of synthetic approaches to substituted and functionalized carbazoles have been reported over the years. They have been periodically reviewed with emphasis on two general problems: regiochemistry and *N*-protection.[4–6] A few years ago, we introduced the anionic annulation of furoindolones in the regioselective synthesis of carbazoles.[7] The underlying principle was Michael-initiated ring closure for the formation of 1-hydroxycarbazoles. We now report that the similar annulation, when judiciously coupled to an ester-driven *para*-Claisen rearrangement and a selective *ortho*-decarboxylation, leads to concise total synthesis of prenylcarbazole alkaloids (Fig. 1). We also report a *m*-CPBA-promoted oxidative cyclization of an *ortho*-prenylcarbazole acid to the 3,4-dihydroisocoumarin motif of clausevatines.

In recent times, the prenylcarbazoles **1–16** (Fig. 1) with densely substituted A-rings, have become attractive synthetic targets because of their profound activities against different cancer cell lines.[8] Clausamines[9] A–D and F have been reported to inhibit EBV activation in Raji cells.[10] The presence of a prenyl group is shown to be beneficial for the bioactivities.[11] Furthermore, a prenyl group is poised to generate structural diversity through various transformations as evident from the co-occurrence of congeners **1–3** and **11–16**. The overall structural features of the target natural products **1–16** (Fig. 1) suggest that an intermediate like **17** (Scheme 1) would give rise to tetracyclic carbazoles **1–3** and **11–16**.

Hence, the sequence consisting of *C*-prenylation, annulation and selective decarboxylation made up the essence of our investigations. The intermediate **17** was thought to be obtainable from tetrasubstituted carbazole **18** *via* selective removal of the CO_2Me group at C-2. The requisite carbazole diester **18** was expected to be assembled by Sammes annulation[12] of furoindolone **19** with dimethyl maleate. Elaboration of the pendant prenyl group of the carbazole **17** through an oxidation should result in the synthesis of the natural products such as **1–3** and **11–16**.

The study began with readily accessible furoindolone **20**[7] (Scheme 2), after initial hurdles with its *N*-MOM and *N*-Boc analogues. Indolone **21** was prepared in 87% yield by LDA mediated prenylation of **20** and then submitted to annulation with dimethyl maleate in the presence of LDA to obtain carbazole diester **22**. Contrary to our expectation, the efficacy of the annulation of **21** was not encouraging, giving the desired product **22** in only 10–15% yield. The yield slightly improved with TMEDA as the additive. We were, however, not daunted by the results in view of anomalous reactivities encountered in similar anionic annulations.[13]

In the revised plan, installation of the requisite prenyl group was postponed until the annulation of the furoindolone **20** with dimethyl maleate *i.e.* preparation of **23** was undertaken before that of **22**. Accordingly, the annulation of **20** with dimethyl maleate was performed to give the corresponding product **23** in 47% yield. The highest yield (68%) of **23** was obtained with the combined use of lithium *tert*-butoxide (LTB) and TMEDA. Etherification of **23** with K_2CO_3 and prenyl bromide afforded ether **24** in 71% yield (Scheme 3).[14] *para*-Claisen rearrangement[15] of the prenyl ether **24** in refluxing *N*,*N*-dimethylaniline (DMA) occurred desirably in 10 min to give tetrasubstituted carbazole **22** in 65% yield. This was characterized as its acetate **25**. The selective demethoxycarbonylation of the C-2 CO_2Me group in **22** was studied next. This transformation turned out to be more difficult than

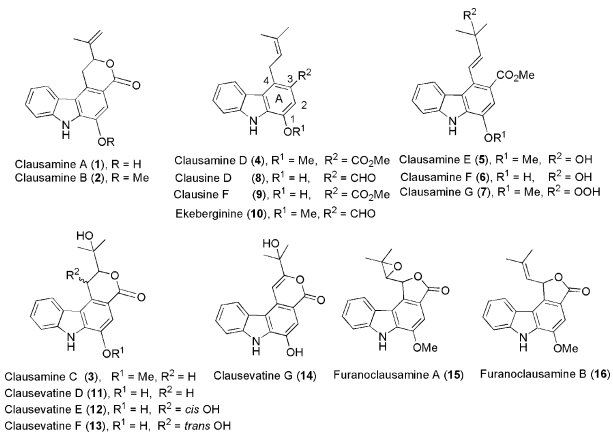

Fig. 1 Structures of prenylcarbazoles and congeners.

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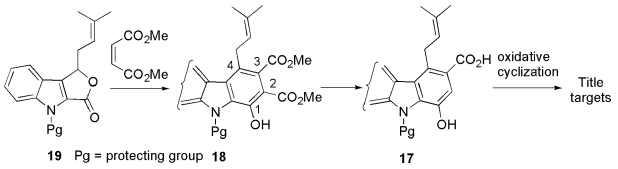
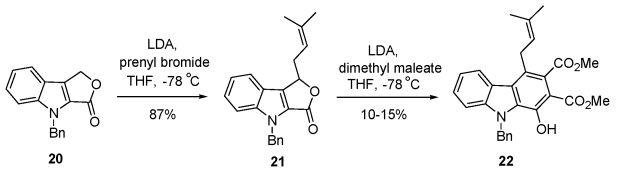
† Electronic supplementary information (ESI) available: Spectral data and experimental procedures for all new compounds reported herein. CCDC 770961. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc00527d



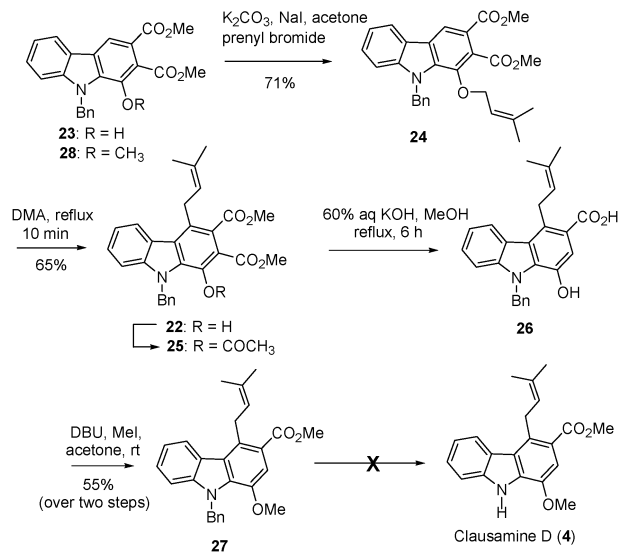
Scheme 1 Initial plan for the synthesis of prenylcarbazoles.



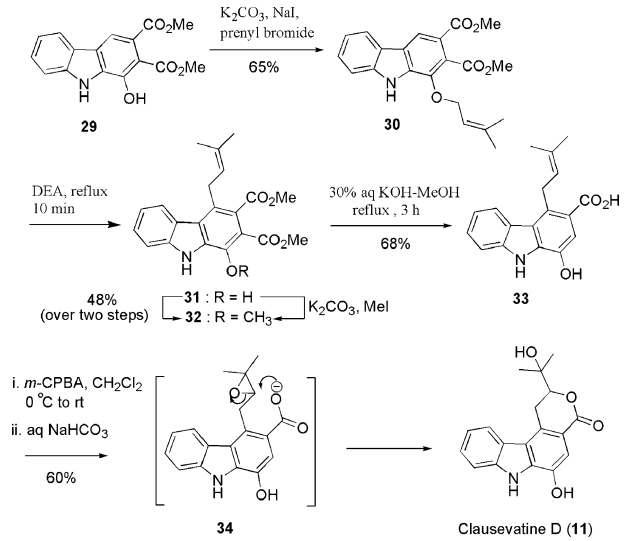
Scheme 2 Sammes annulation of 1-prenylfuroindolone.

we anticipated. It was found to proceed most effectively only with 60% aq KOH in methanol at reflux. The crude hydroxy acid **26** was transformed to methyl ester **27** (55% over two steps) by treatment with DBU-CH_3I[16] in acetone at rt. The structure of the product **27** was unequivocally established by X-ray crystallographic analysis. Unfortunately, the desired selective *N*-debenzylation[17] of the prenylcarbazole **27** to clausamine D (**4**) proved to be a major obstacle to the total synthesis. Anticipating that the nucleophilic reactivity of the *C*-prenyl group was the source of such problems, we considered *N*-debenzylation[18] of **28** before installation of the prenyl group. With anhyd $AlCl_3$, both benzyl and methyl groups of **28** were removed and hydroxycarbazole **29** was obtained in 78% yield.

With **29** in hand, we exploited the differential reactivity of the phenolic OH and the carbazole NH to secure selective prenylation (Scheme 4). Under very stringent conditions and careful monitoring of the reaction, we were able to prepare *O*-prenyl derivative **30**. The reaction of carbazole **29** with K_2CO_3 and prenyl bromide at rt for 1.5 h afforded *O*-prenylated derivative **30** in 65% yield. An excess amount of K_2CO_3 or prolonged reaction time was detrimental to the



Scheme 3 Prenylation and selective demethoxycarbonylation.



Scheme 4 Synthesis of clausevatine D.

reaction. When *O*-prenyl carbazole **30** was heated in refluxing DEA for 10 min, the *para*-Claisen rearrangement product **31** was obtained, which was converted to its methyl ether **32** in 48% yield (over two steps). For achieving demethoxycarbonylation at C-2 of diester **31**, we examined the reaction under various conditions. The optimized condition was 30% aq KOH in refluxing MeOH that worked well to give hydroxy acid **33** in 68% yield. Without further purification, the crude acid was converted to clausine F[19](**9**) in 76% yield by treatment with DBU-MeI. *O*- Methylation of **9** with K_2CO_3-MeI in acetone afforded another natural product, *i.e.* clausamine D (**4**) in 72% yield. The spectroscopic data of both the synthesized compounds **4** and **9** matched well with the reported values.[10,19] This synthesis of both clausine F (**9**) and clausamine D (**4**) constitutes the first synthesis.

For the construction of the dihydroisocoumarin unit of clausevatine D[20] (**11**), dihydroxylation of the pendant prenyl group of the carbazole acid **33** was attempted using the protocol[8b] of Lebold and Kerr. But, the result was an intractable mixture of products. On the other hand, treatment of the acid **33** with *m*-CPBA in CH_2Cl_2 followed by work-up with aq $NaHCO_3$ serendipitously gave a 60% yield of clausevatine D (**11**) through an unprecedented oxidative cyclization. To our knowledge, such formation of a dihydroisocoumarin is not reported in the literature.[21] The closest analogy is found in the formation of a δ-lactone by cyclization of a crude 1,2-disubstituted epoxide with an open-chain acid under reflux in toluene or in the presence of camphor sulfonic acid.[22] The exceptional nucleophilicity of the aromatic carboxylate ion in **34**, supposedly formed during work-up, could be due to phenylogous α-effect of the carbazole N. The expected formation of the oxepane ring through formation of tertiary carbocation from **33** under the influence of *m*-CPBA was not encountered. With *O*-methylation of compound **11** with K_2CO_3-MeI in acetone in 77% yield, the total synthesis of the tetracyclic natural product, clausamine C (**3**) was completed.

In conclusion, a notably brief and regiospecific tactic has been developed for the synthesis of prenylcarbazoles and their congeners. An unusual oxidative cyclization, a selective removal

of methoxycarbonyl group and a *p*-Claisen rearrangement serve as the key steps for the total synthesis of clausamine C and clausevatine D. The developed route has been successfully implemented in the first total synthesis of clausine F and clausamine D. Further extension of this strategy to the asymmetric synthesis of clausevatine D and furanoclausamines is underway.

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Notes and references

1 (*a*) H.-J. Knölker and K. R. Reddy, *Chem. Rev*., 2002, **102**, 4303–4427; (*b*) D. P. Chakraborty, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, New York, 1993, vol. 44, p. 257, and references therein; (*c*) H.-J. Knölker, *Curr. Org. Synth*., 2004, **1**, 309–331; (*d*) H.-J. Knölker, *Top. Curr. Chem*., 2005, **244**, 115–148; (*e*) H.-J. Knölker and K. R. Reddy, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, Amsterdam, 2008, vol. 65, pp. 1–430.

2 *Organic Light Emitting Devices: Synthesis, Properties, and Applications*, ed. K. Müllen and U. Scherf, Wiley-VCH, Weinheim, Germany, 2006.

3 (*a*) D. Crich and S. Rumthao, *Tetrahedron*, 2004, **60**, 1513–1516; (*b*) H.-Y. Cheng, C. S. Randall, W. W. Holl, P. P. Constantinides, T.-L. Yue and G. Z. Feuerstein, *Biochim. Biophys. Acta, Biomembr*., 1996, **1284**, 20–28; (*c*) R. Kumar, U. Ramachandran, K. Srinivasan, P. Ramarao, S. Raichur and R. Chakrabarti, *Bioorg. Med. Chem*., 2005, **13**, 4279–4290.

4 (*a*) L. Ackermann and A. Althammer, *Angew. Chem., Int. Ed*., 2007, **46**, 1627–1629; (*b*) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck and M. J. Gaunt, *J. Am. Chem. Soc*., 2008, **130**, 16184–16186; (*c*) K. E. Knott, S. Auschill, A. Jager and H.-J. Knölker, *Chem. Commun*., 2009, 1467–1469; (*d*) M. E. Buden, V. A. Vaillard, S. E. Martin and R. A. Rossi, *J. Org. Chem*., 2009, **74**, 4490–4498; (*e*) M. Hussain, D. T. Tung and P. Langer, *Synlett*, 2009, 1822–1826; (*f*) T. Watanabe, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem*., 2009, **74**, 4720–4726; (*g*) K. 1. Thevissen, A. Marchand, P. Chaltin, E. M. K. Meert and B. P. A. Cammue, *Curr. Med. Chem*., 2009, **16**, 2205–2211; (*h*) V. Sridharan, M. A. Martin and J. C. Menendez, *Eur. J. Org. Chem*., 2009, 4614–4621.

5 (*a*) W. Q. Kong, C. L. Fu and S. M. Ma, *Chem. Commun*., 2009, 4572–4574; (*b*) C. Ito, M. Itoigawa, K. Aizawa, K. Yoshida, N. Ruangrungsi and H. Furukawa, *J. Nat. Prod*., 2009, **72**, 1202–1204; (*c*) S. Tohyama, T. Choshi, S. Azuma, H. Fujioka and S. Hibino, *Heterocycles*, 2009, **79**, 955–965; (*d*) N. Ramesh, G. G. Rajeshwaran and A. K. Mohanakrishnan, *Tetrahedron*, 2009, **65**, 3592–3602; (*e*) C. N. Della, G. Sassi and M. Catellani, *Adv. Synth. Catal*., 2008, **350**, 2179–2182; (*f*) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng and S. L. Buchwald, *J. Org. Chem*., 2008, **73**, 7603–7610; (*g*) J. T. Kuethe and K. G. Childers, *Adv. Synth. Catal*., 2008, **350**, 1577–1586; (*h*) Z. J. Liu and R. C. Larock, *Tetrahedron*, 2007, **63**, 347–355.

6 (*a*) J. S. Russel, E. T. Pelkey and S. J. P. Yoon-Miller, *Progress in Heterocyclic Chemistry*, 2009, vol. 21, pp. 145–178; (*b*) H.-J. Knölker, *Chem. Lett*., 2009, **38**, 8–13; (*c*) S. Agarwal, S. Cammerer, S. Filali, W. Frohner, J. Knoll, M. P. Krahl, K. R. Reddy and H.-J. Knölker, *Curr. Org. Chem*., 2005, **9**, 1601–1614.

7 D. Mal, B. K. Senapati and P. Pahari, *Tetrahedron*, 2007, **63**, 3768–3781.

8 (*a*) M. R. Naffziger, B. O. Ashburn, J. R. Perkins and R. G. Carter, *J. Org. Chem*., 2007, **72**, 9857–9865; (*b*) T. P. Lebold and M. A. Kerr, *Org. Lett*., 2008, **10**, 997–1000; (*c*) T. P. Lebold and M. A. Kerr, *Org. Lett*., 2007, **9**, 1883–1886; (*d*) R. Forke, M. P. Krahl, T. Krause, G. Schlechtingen and H.-J. Knölker, *Synlett*, 2007, 268–272; (*e*) M. P. Krahl, A. Jager, T. Krause and H.-J. Knölker, *Org. Biomol. Chem*., 2006, **4**, 3215–3219; (*f*) H.-J. Knölker and F. Wolfgang, *Synlett*, 1997, 1108–1110; (*g*) H.-J. Knölker, W. Fröhner and A. Wagner, *Tetrahedron Lett*., 1998, **39**, 2947–2950; (*h*) H.-J. Knölker and K. R. Reddy, *Synlett*, 1999, 596–598; (*i*) H.-J. Knölker, E. Baum and K. R. Reddy, *Tetrahedron Lett*., 2000, **41**, 1171–1174; (*j*) R. Czerwonka, K. R. Reddy, E. Baum and H.-J. Knölker, *Chem. Commun*., 2006, 711–713; (*k*) W. Frohner, K. R. Reddy and H.-J. Knölker, *Heterocycles*, 2007, **74**, 895–912.

9 C. Ito, S. Katsuno, N. Ruangrungsi and H. Furukawa, *Chem. Pharm. Bull*., 1998, **46**, 344–346.

10 C. Ito, S. Katsuno, M. Itoigawa, N. Ruangrungsi, T. Mukainaka, M. Okuda, Y. Kitagawa, H. Tokuda, H. Nishino and H. Furukawa, *J. Nat. Prod*., 2000, **63**, 125–128.

11 C. Ito, M. Itoigawa, A. Sato, C. M. Hasan, M. A. Rashid, H. Tokuda, T. Mukainaka, H. Nishino and H. Furukawa, *J. Nat. Prod*., 2004, **67**, 1488–1491.

12 (*a*) N. J. P. Broom and P. G. Sammes, *J. Chem. Soc., Chem. Commun*., 1978, 162–164; (*b*) D. Mal and P. Pahari, *Chem. Rev*., 2007, **107**, 1892–1918.

13 (*a*) J. J. Sperry, T. Y. Yuen and M. A. Brimble, *Synthesis*, 2009, 2561–2569; (*b*) N. P. H. Tan and C. D. Donner, *Tetrahedron Lett*., 2008, **49**, 4160–4162.

14 Mitsunobu etherification of carbazole **26** with prenyl alcohol was unsuccessful.

15 (*a*) X. Lei, M. Dai, Z. Hua and S. J. Danishefsky, *Tetrahedron Lett*., 2008, **49**, 6383–6385; (*b*) A. S. R. Anjaneyulu and B. M. Isaa, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2089–2094; (*c*) A. M. Martin Castro, *Chem. Rev*., 2004, **104**, 2939–3002.

16 D. Mal, A. Jana, S. Ray, S. Bhattacharya, A. Patra and S. R. De, *Synth. Commun*., 2008, **38**, 3937–3946.

17 The established methods for *N*-debenzylation such as O_2-KTB- DMSO, $AlCl_3$ and TFA-TfOH did not work out. With O_2-KTB-DMSO, the corresponding carboxylic acid was obtained in 69% yield.

18 For the *N*-debenzylation of **28**, the standard reagents: (i) NBS, NMA, (ii) CAN, (iii) IBX, (iv) $ClCO_2Et$, (v) Me_3SiCl and NaI, (vi) $BF_3{\cdot}OEt_2$, (vii) diisopropyl azodicarboxylate in toluene, (viii) H_2, 10% Pd–C, (ix) Li, $C_{10}H_8$, (x) Na/ liq. NH_3 failed to afford the desired product *i.e*. *N*-debenzylated analog of **28**.

19 T.-S. Wu and S.-C. Huang, *Chem. Pharm. Bull*., 1992, **40**, 1069–1071.

20 T.-S. Wu, S.-C. Huang and P.-L. Wu, *Chem. Pharm. Bull*., 1998, **46**, 1459–1461.

21 H. Hamamoto, Y. Suzuki, H. Takahashi and S. Ikegam, *Adv. Synth. Catal*., 2007, **349**, 2685–2689.

22 (*a*) Q. Lin, H. Xu, B. Wu, G. Guo and W. Zhou, *Tetrahedron Lett*., 1985, **26**, 1233–1236; (*b*) M. Ochiai, T. Ukita, S. Iwaki, Y. Nagao and E. Fujita, *J. Org. Chem*., 1989, **54**, 4832–4840.