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Total syntheses of the fungal metabolites (±)-acremines A, B and I

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ABSTRACT

A concise and diversity-oriented approach, incorporating elements of regio- and stereocontrol, to the recently isolated bioactive polyoxygenated cyclohexanoid natural products acremines A, B and I, from commercially accessible building blocks, is outlined.

Endophytic fungi, growing interactively within the complex biological milieu of their plant host, but without any overtly deleterious effects, are known to be a rich source of biologically active secondary metabolites.[1] The genus *Acremonium* has been found to harbor diverse classes of natural products with wide ranging bioactivity profiles.[2] An Italian group[3] has investigated a strain of *Acremonium bissoides*, named A20 and isolated from grapevine leaves inoculated with *Plasmopara veticola*, for new metabolites. From the cultures of this A20 fungus, a series of novel and closely related metabolites named acremines A–F (**1–6**),[3a,4–6] G (**7**),[3b] and H, I, L–N (**8–12**)[3c] were isolated and their stereostructures were determined through NMR studies, single crystal X-ray structure determination, and application of Mosher's method (Fig. 1).[3]

Acremines **1–12** are quite interesting biosynthetically as they arise through interplay of polyketide and mevalonate pathways. In addition, they embody dense and varied substitution and oxygenation patterns on a cyclohexanoid platform replete with attendant stereochemical intricacies.

Acremines in general are known to inhibit the growth of sporangia in *P. veticola*, and some also exhibit mild cytotoxic activity against the H460 tumor cell line.[3] For reasons of structural novelty and interesting bioactivity, we became interested in the total syntheses of this family of natural products and describe herein the first total syntheses of the monomeric acremines A, B, and I employing a common and flexible synthetic methodology.[7]

The oxygenated cyclohexanoid core present in acremines A (**1**), B (**2**), and in particular the epoxide moiety in acremine I (**9**) is reminiscent of epoxyquinone natural products, a bioactive class of compounds,[8] whose syntheses had engaged our attention, and toward which we developed a general approach[9] emanating from the readily available Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone. Our instinct therefore was to devise a tactical adaptation of this established and versatile protocol toward acremines A, B, and I.

Thus, our strategy toward **1**, **2,** and **9** started from the Diels–Alder adduct, **13**,[10] of cyclopentadiene and 2-methyl-*p*-benzoquinone. Nucleophilic epoxidation of **13** was stereoselective and straightforward and furnished the epoxyquinone **14**, Scheme 1. Base-mediated hydroxymethylation of **14** was both regio- and stereoselective, in agreement with our earlier observations with similar systems, and readily led to **15**. Reduction of **15** with excess DIBAL-H was regio- and stereoselective, and delivered diol **16**. The observed selectivity was engendered through a co-ordination of the aluminum of DIBAL-H with the hydroxy and epoxy oxygens in **15**, and subsequent delivery of the hydride from the α-face. Retro Diels–Alder reaction in **16**, under thermal activation, disengaged the cyclopentadiene moiety and furnished the key functionally embellished cyclohexanoid intermediate **17**. TEMPO-CuCl-mediated chemoselective oxidation of diol **17** under the mild Semmelhack conditions[11] led to the labile hydroxy aldehyde **18** which was directly subjected to Wittig–Horner olefination to furnish **19**. After exploratory forays toward the targets **1** and **2** directly from **19**, it became clear that the cyclohexenone carbonyl group at C1 needed to be protected first. Consequently, **19** was readily converted into the ketal **20**. Addition of methyllithium to the ester moiety was now straightforward and delivered **21**[12] with the requisite tertiary hydroxy group bearing side chain. The functionally embellished epoxide **21** was now poised to serve as a common intermediate for the target natural products acremines A, B, and I.

MnO_2 oxidation of the allylic hydroxy group in **21** furnished the enone **22** and set the stage for the regio-selective reductive opening of the epoxide ring. In the event, exposure of **22** to in situ-generated 'PhSeH'[13] led to the tertiary diol **23**,[12] Scheme 2. Luche reduction[14] of the C4 carbonyl in the enone **23** furnished a diastereomeric mixture (5:1) of **24a** (4α-hydroxy) and **24b** (4β-hydroxy) triols. Careful ketal deprotection of **24a,b** led to acremine A (**1**)[12] and *epi*-acremine A (**25**), Scheme 2. The spectral (^1H and ^{13}C NMR) data of our synthetic **1** were found to be in complete agreement with those reported for the natural product.[3a,5] The synthesis of acremine B turned out to be quite straightforward. The advanced intermediate **23** on ketal deprotection under a carefully controlled

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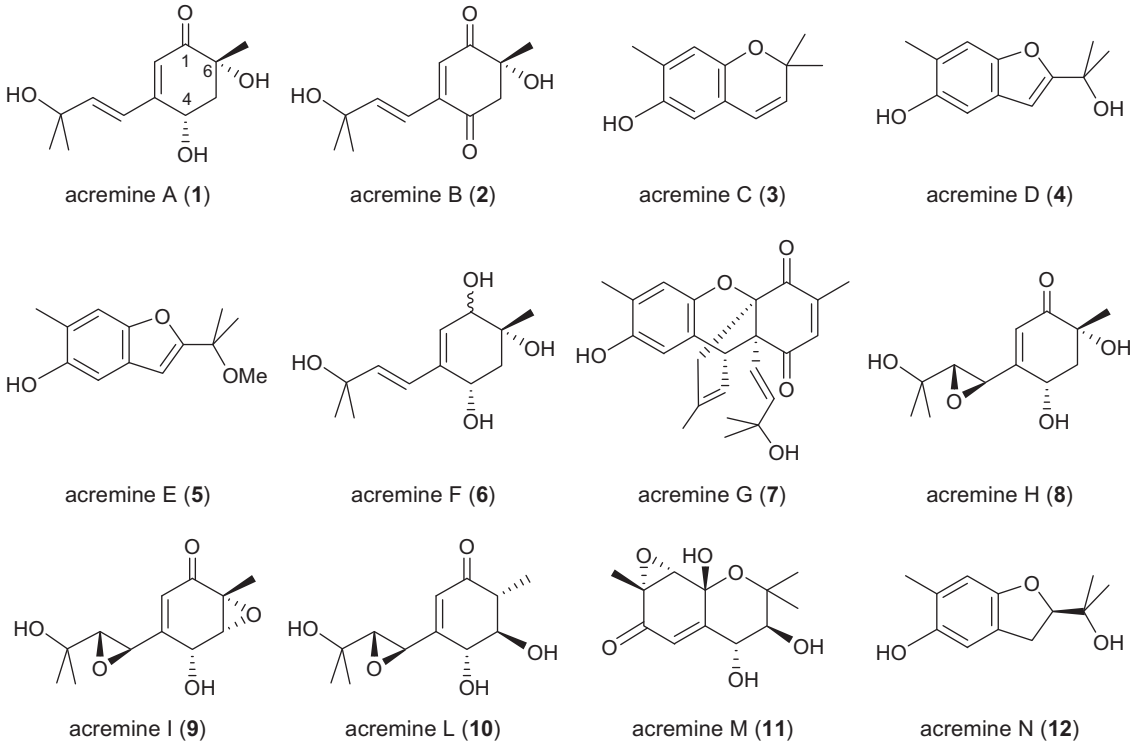
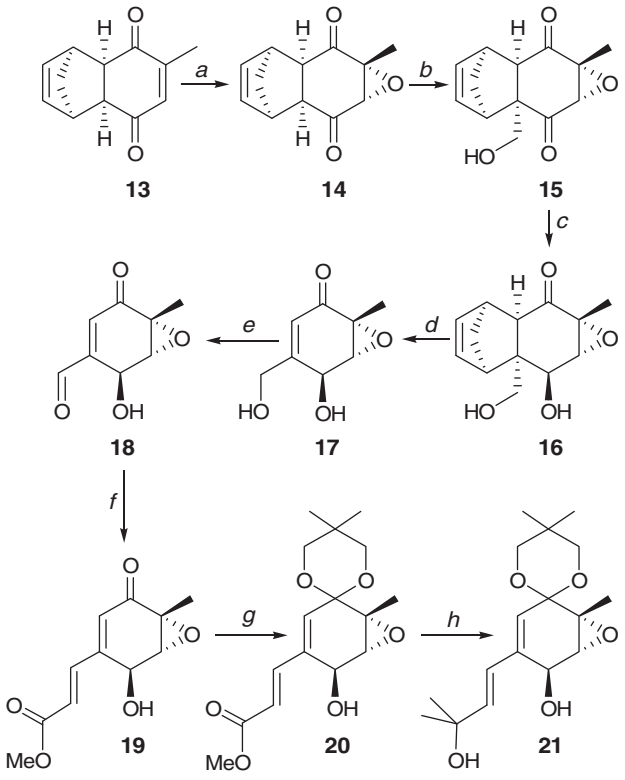
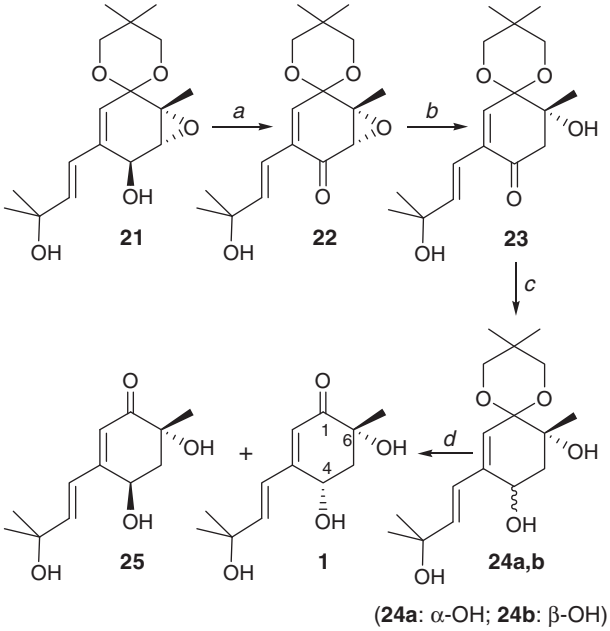


Figure 1.



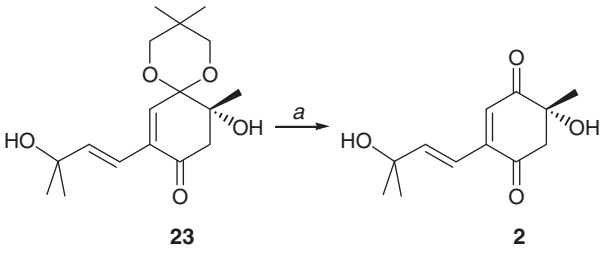
Scheme 1. Reagents and conditions: (a) 10% Na_2CO_3, 30% H_2O_2, acetone, 0 °C, 2 h, 88%; (b) 35% formalin, DBU (0.1 equiv), THF, 0 °C, 2 h, 81%; (c) DIBAL-H (2.1 equiv), THF, −80 °C, 5 h 60% (based on recovered starting material); (d) diphenyl ether, 210 °C, 10 min, 75%; (e) TEMPO, O_2, CuCl, DMF, rt, 4 h; (f) $Ph_3P=CHCO_2Me$, benzene, rt, 6 h, 80% (after two steps); (g) 2,2-dimethyl-1,3-propanediol, PPTS, benzene, reflux, 12 h, 66%; (h) MeLi (5 equiv), THF, −78 °C, 30 min, 60%.



Scheme 2. Reagents and conditions: (a) MnO_2, CH_2Cl_2, rt, 6 h, 80%; (b) Ph_2Se_2, $NaBH_4$, EtOH, AcOH, 0 °C, 1 h, 65%; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt, 45 min, 70%; (d) Amberlyst 15, moist acetone, rt, 15 min, 72% overall (**1** = 60%, **25** = 12%).

regime led to the natural product **2**[12] whose spectral data were identical with those reported by the Italian group, Scheme 3.[3a]

In the natural product acremine I (**9**), the epoxyquinone moiety remains intact and the main challenge, from the synthetic point of view, is the installation of the second epoxide ring on to the 5C side chain with stereocontrol in order to secure the requisite relative



Scheme 3. Reagents and condition: (a) Amberlyst 15, moist acetone, rt, 30 min, 80%.

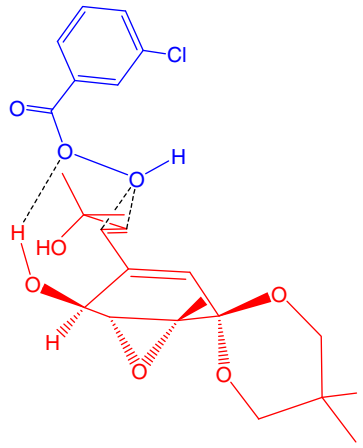
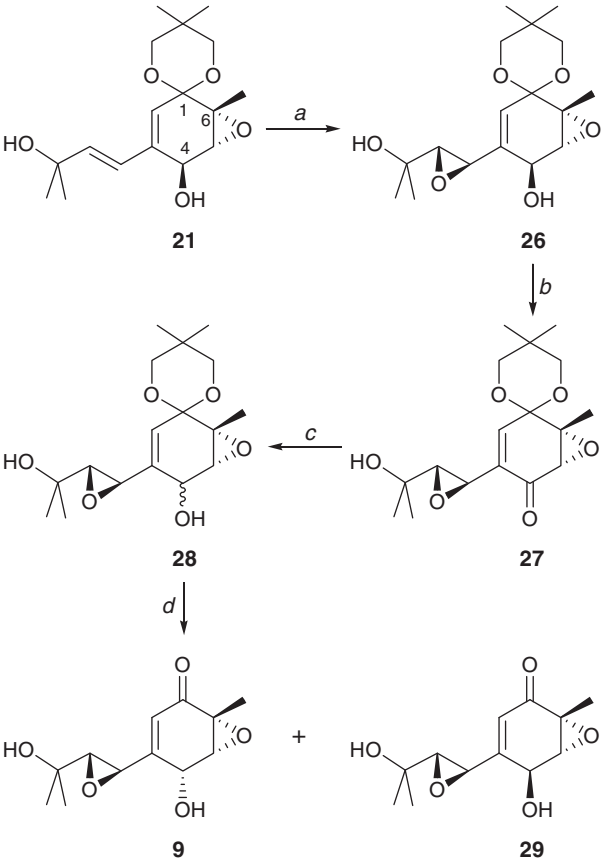


Figure 2. A schematic representation of the diastereoselectivity directed by the distal 4β-hydroxy group in the *m*CPBA mediated epoxidation of **21**.



Scheme 4. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, 0 °C, 2 h, 80%; (b) MnO_2, CH_2Cl_2, rt, 4 h, 75%; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH rt, 45 min, 72%; (d) Amberlyst 15, moist acetone, rt, 15 min, 90% overall (**9** = 45%, **29** = 45%).

stereochemistry of the two epoxide rings. To address this issue, we contemplated exploiting hydroxy-directed peracid epoxidation as a stratagey for the stereoselective delivery of the epoxide ring. It was indeed with this intent that the advanced intermediate **21** with a 4β-hydroxy group was crafted. Exposure of **21** to *m*-chloroperbenzoic acid proceeded with high diastereoselectivity, directed as envisaged by the strategically positioned distal 4β-hydroxy group (Fig. 2), to furnish the diepoxide **26**,[12] Scheme 4.

At this stage the 4β-hydroxy group in **26**, having discharged its strategic role, needed to be inverted to correspond to the stereochemical disposition present in the natural product **9**. Our initial idea was to effect this inversion of the 4-hydroxy group in **26** directly through Mitsunobu reaction,[15] or its various modifications. However, in practice, all such attempts proved unproductive and we were forced to adopt a more circuitous approach. Consequently, the allylic 4-hydroxy group was oxidized with MnO_2 to furnish diepoxyenone **27**, Scheme 4. Luche reduction of **27** led to a diastereomeric mixture **28** (1:1) of 4α- and 4β-stereoisomers. Ketal deprotection in **28** was carefully carried out to furnish the readily separable acremine I (**9**)[12] and 4-*epi* acremine I (**29**), Scheme 4. The spectral data (^1H and ^{13}C NMR) of **9** matched with those reported for the natural product.[16]

In summary, a flexible general approach to recently reported bioactive polyoxygenated cyclohexanoid natural products acremines from the readily available Diels–Alder adduct of cyclopentadiene and 2-methyl-*p*-benzoquinone has been delineated. Appropriate adaptation of this strategy should enable access to other acremine related fungal metabolites.

Acknowledgments

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12. All new compounds reported here are racemic and were characterized on the basis of spectroscopic data (IR, ^1H, ^{13}C NMR and HRMS). Spectral data for some

of the key compounds are as follows: Compound **21** IR (neat): ν_{max} 3401, 2960, 2931, 2870, 1107, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.31 (d, J = 16 Hz, 1H), 6.29 (s, 1H), 6.16 (d, J = 16 Hz, 1H), 4.59 (s, 1H), 3.91 (d, J = 12 Hz, 1H), 3.73 (d, J = 11 Hz, 1H), 3.53 (dd, J = 12 Hz, 3 Hz, 1H), 3.40 (d, J = 3 Hz, 1H), 3.36 (dd, J = 11 Hz, 2 Hz, 1H), 1.58 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H) 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 136.2, 124.6, 117.9, 94.9, 71.2, 71.0, 70.4, 65.5, 62.4, 61.7, 30.1, 29.9, 29.7, 23.1, 22.2, 15.4; HRMS (ES): m/z calcd for $C_{17}H_{26}O_5$ $(M+Na)^+$: 333.1678, found: 333.1660. Compound **23** IR (neat): ν_{max} 3400, 2919, 2851, 1679, 1558, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H), 6.49 (d, J = 16 Hz, 1H), 6.40 (d, J = 16 Hz, 1H), 3.91 (d, J = 12 Hz, 1H), 3.79 (d, J = 12 Hz, 1H), 3.56 (dd, J = 12 Hz, 2 Hz, 1H), 3.48 (dd, J = 11 Hz, 3 Hz, 1H), 2.75 (d, J = 17 Hz, 1H), 2.68 (d, J = 17 Hz, 1H), 2.52 (s, 1H), 1.38 (s, 6H), 1.37 (s, 3H), 1.25 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 142.0, 136.1, 133.6, 119.9, 96.0, 75.9, 71.3 (2C), 71.1, 48.6, 30.2, 29.7 (2C), 22.9, 22.0 (2C); HRMS (ES): m/z calcd for $C_{17}H_{26}O_5$ $(M+Na)^+$: 333.1678, found: 333.1632. Compound **26** IR (neat): ν_{max} 3436, 2956, 2925, 2870, 1107, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.25 (s, 1H), 4.58 (s, 1H), 3.88 (d, J = 12 Hz, 1H), 3.68 (d, J = 11 Hz, 1H), 3.59 (s, 1H), 3.48 (dd, J = 11 Hz, 2 Hz, 1H), 3.37–3.32 (m, 2H), 2.81 (d, J = 2 Hz, 1H), 1.57 (s, 3H), 1.28 (s, 6H), 1.24 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 114.3, 95.0, 71.2, 70.4, 68.3, 68.2, 66.3, 61.8, 60.7, 30.1, 29.6, 26.9, 25.1, 23.1, 22.1, 15.3; HRMS (ES): m/z calcd for $C_{17}H_{26}O_6$ $(M+Na)^+$: 349.1627, found: 349.1624. (±)-Acremine A (**1**) IR (neat): ν_{max} 3377, 2964, 2925, 2853, 1661, 1634 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ 6.67 (d, J = 16 Hz, 1H), 6.46 (d, J = 16 Hz, 1H), 5.92 (s, 1H), 4.65–4.62 (m, 1H), 2.31 (dd, J = 14 Hz, 5 Hz, 1H), 2.11 (dd, J = 14 Hz, 7 Hz, 1H), 1.31 (s, 6H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 200.7, 159.6, 148.0, 124.5, 122.6, 73.3, 70.8, 66.1, 45.5, 29.2 (2C), 24.8. HRMS (ES): m/z calcd for $C_{12}H_{18}O_4$ $(M+Na)^+$: 249.1103, found: 249.1073. (±)-Acremine B (**2**) IR (neat): ν_{max} 3429, 2974, 2925, 1682, 1130 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.81 (d, J = 16 Hz, 1H), 6.76 (s, 1H), 6.54 (d, J = 16 Hz, 1H), 3.14 (d, J = 15 Hz, 1H), 3.05 (d, J = 15 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 195.4, 149.4, 147.8, 129.9, 118.4, 75.1, 71.4, 53.1, 29.6 (2C), 27.6; HRMS (ES): m/z calcd for $C_{12}H_{16}O_3$ $(M+Na)^+$ 247.0946 found: 247.0947. (±)-Acremine I (**9**) IR (neat): ν_{max} 3284, 2926, 2854, 1656, 1017 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ 5.90 (s, 1H), 5.20 (d, J = 9 Hz, 1H), 4.52 (d, J = 8 Hz, 1H), 3.70 (d, J = 2 Hz, 1H), 3.11 (d, J = 2 Hz, 1H), 1.40 (s, 3H), 1.24 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 194.4, 155.8, 122.2, 68.8, 68.2, 63.9, 63.4, 58.2, 53.9, 26.8, 25.9, 14.9; HRMS (ES): m/z calcd for $C_{12}H_{16}O_5$ $(M+Na)^+$: 263.0895, found: 263.0899.

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