Hot off the Press

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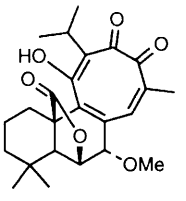
Reviewing the recent literature on natural products and bioorganic chemistry

A C_{23} terpenoid **1** with a new hassane skeleton has been isolated from *Salvia apiana* (J. G. Luis *et al.*, *Tetrahedron*, 1996, *52*, 12309). The hassane **1** is related to the apianes recently isolated from the same species [see 'Hot off the Press' in *Nat. Prod. Rep.*, 1996, *13*(5), iii] and the authors propose a common biogenetic origin from an abietane. Neovibsanine A **2** from *Viburnum awabuki* is an unusual cleaved diterpenoid (Y. Fukuyama *et al.*, *Tetrahedron Lett.*, 1996, *37*, 6767). The co-occurring vibsanine B **3** has been converted photochemically into the neovibsanine skeleton. Caryose **4** is the first example of a carbocyclic monosaccharide from *Pseudomonas caryophylli* (M. Adinolfi, *Carbohydr. Res.*, 1996, *284*, 111). A new class of carbon skeleton **5** has been identified from the poison gland of the African Myrmicaria ant (F. Schroder *et al.*, *Chem. Commun.*, 1996, *18*, 2139); consisting of two unbranched C15 chains it has been called myrmicarin 430A. Dermatolactone **6** from the Basidiomycete *Irpex lacteus* has a new sesquiterpenoid carbon skeleton that is probably related to the illudane group (A. Mayer *et al.*, *Phytochemistry*, 1996, *43*, 375). An unusual spiroether, cleroindicin A **7**, has been isolated from *Clerodendrum indicum* (J. Tian *et al.*, *Chin. Chem. Lett.*, 1996, *7*, 279).

Nostocine A **8** is a violet pigment produced as an extracellular metabolite from the freshwater cyanobacterium *Nostoc spongiaeforme* (K. Hirata *et al.*, *Heterocycles*, 1996, *43*, 1513). The structure of this nitrogen-rich heterocycle was established by X-ray analysis. Nostocine A **8** shows growth inhibitory activity against a range of organisms and it is suggested that nostocine A **8** plays an allelopathic role. Fischerellin A **9**, from the cyanobacterium *Fischerella muscicola*, also shows interesting allelopathic activity as a fungicide and as a photosystem II inhibitor (L. Hagmann and F. Jüttner, *Tetrahedron Lett.*, 1996, *37*, 6539). S. Sepúlveda-Boza and B. K. Cassels have reviewed the plant metabolites that are active against trypanosomiasis due to *Trypanosoma cruzi* (*Planta Med.*, 1996, *62*, 98). A. D. Wright and co-workers have reviewed their search for marine-derived natural products with selective antimalarial activity. (*J. Nat. Prod.*, 1996, *59*, 710).

There have been a number of syntheses reported recently that have resulted in the review of the structure of the target natural product. **The structure of bruceoside** C, a quassinoid from *Brucea javanica*, **has been shown to be incorrect.** P. A. Grieco and co-worker synthesized the alleged aglycone of bruceoside C and found that it was not identical to the aglycone derived from the natural product (*J. Org. Chem.*, 1996, *61*, 5316). The correct structure for bruceoside C has not yet been established. The structure assigned to a clerodadienoic acid from *Eperua purpurea* has also been shown to be incorrect. T.-H. Lee and C.-C. Liao have synthesized the clerodadienoic acid **10** and



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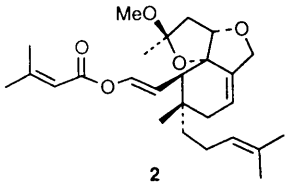

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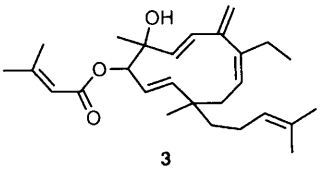

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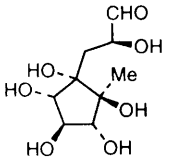

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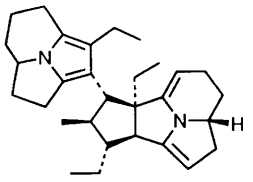

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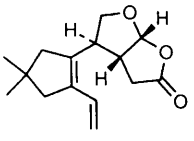

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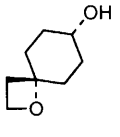

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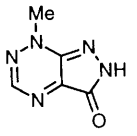

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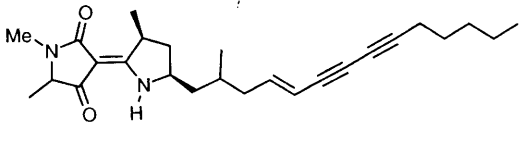

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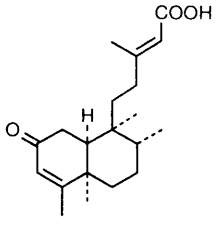

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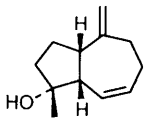

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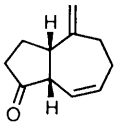

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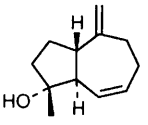

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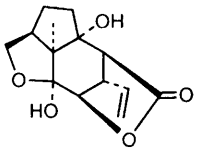
confirmed its structure by X-ray analysis but the spectral data did not agree with those of the natural product (*Tetrahedron Lett.*, 1996, *37*, 6869). T. Koike *et al.* claim to have synthesised dictamnol with the *cis*-fused ring junction **11** (*Chem. Pharm. Bull*, 1996, *44*, 646). However, A. de Groot and co-workers have also synthesized *cis*-dictamnol **11** and report that it is not identical to natural dictamnol (*Chem. Pharm. Bull.*, 1996, *44*, 1400). De Groot's group point out that the synthetic route used by Koike's group involved the ketone intermediate **12** which will readily undergo epimerization to the *trans*-fused junction, and that the **structure of natural dictamnol should be revised to *trans*-dictamnol 13**.



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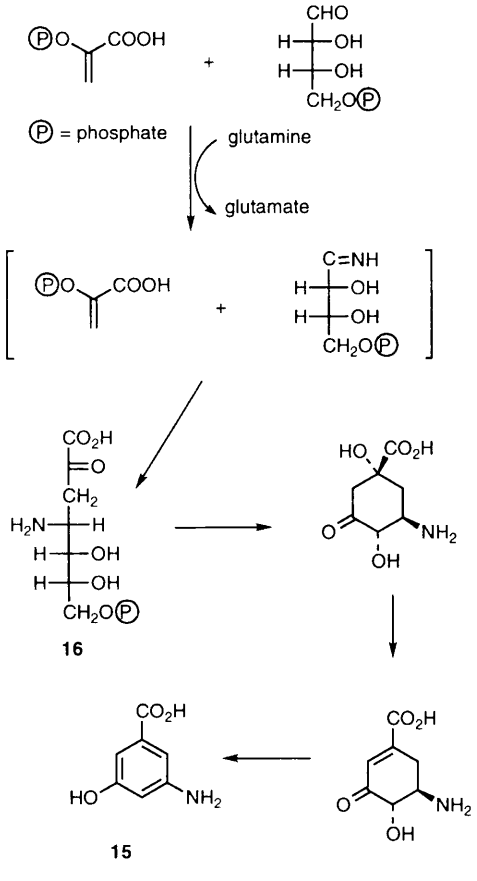

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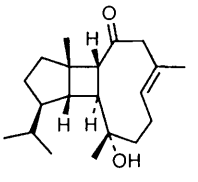
Scheme 1

The biogenesis of sapidolide A **14** from *Baccaurea sapida* is intriguing (N. C. Barua and co-workers, *Tetrahedron Lett.*, 1996, *37*, 6791). The structure of sapidolide A **14** was confirmed by X-ray analysis. H. G. Floss and co-workers have studied the biosynthesis of 3-amino-5-hydroxybenzoic acid **15**, the precursor of the mC_7N units in the ansamycin antibiotics (*J. Am. Chem. Soc.*, 1996, *118*, 7486). Using cell-free extracts from the rifamycin B producer *Amycolatopsis mediterranei* and the ansatrienin A producer *Streptomyces collinus*, they established that 3-amino-5-hydroxybenzoic acid **15** is produced by **a new variant of the shikimate pathway** (**Scheme 1**) involving 4-amino-3,4-dideoxy-D-*arabino*-hepulosonic acid 7-phosphate (amino DAHP) **16** rather than the normal shikimate pathway intermediate 3-deoxy-D-*arabino*-hepulosonic acid 7-phosphate (DAHP).

Deuterium kinetic isotope effects have been used to demonstrate that two different (*S*)-adenosyl-L-methionine: Δ^{24}-sterol methyl transferase enzymes are involved in the biosynthesis of 24(28)-methylenecycloartanol and cyclosadol (24-methylcycloart-23-en-3β-ol) (W. D. Nes and co-workers, *Tetrahedron Lett.*, 1996, *37*, 6823). Sarcoglane **17** from *Sarcophyton glaucum* probably arises by cyclisation of a cembranoid (Y. Kashman and co-workers, *Tetrahedron Lett.*, 1996, *37*, 6909). Sinulariadiolide **18** from a *Sinularia* species also appears to be derived from a cembranoid precursor (Y. Yamada and co-workers, *J. Org. Chem.*, 1995, *60*, 5998). Labelling studies have established that the hydroxy group at C-2′ of bicyclomycin **19** from *Streptomyces sapporonensis* is introduced with inversion of configuration (E.L. Bradley *et al.*, *Tetrahedron Lett.*, 1996, *37*, 6935). The opening of an epoxide intermediate is proposed to explain this inversion. Further evidence for the compartmentalisation of biosynthetic pathways has been presented by C. E. Domenech *et al.* (*Eur. J. Biochem.*, 1996, *239*, 720). They have shown different incorporation of labelled acetate, mevalonate and leucine into sterols, carotenoids and gibberellins in *Gibberella fujikuroi*, suggesting that the biosynthesis is in physically separated compartments with different substrate pools.

The Battersby group have published the synthetic route to the putative spirocyclic pyrrolenone intermediate analogue **20**



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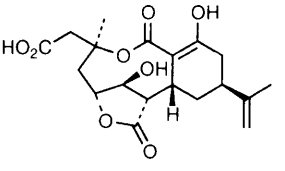

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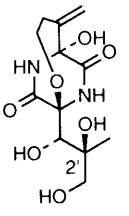

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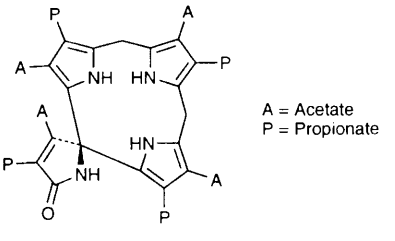

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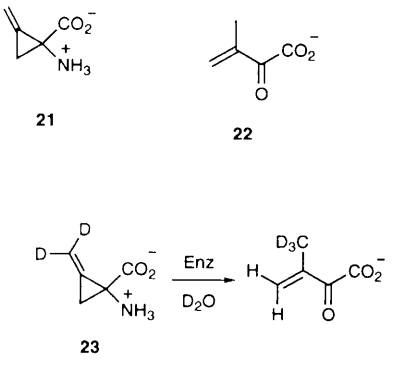
for the reaction of Uroporphyrinogen III synthase, the enzyme that catalyses the formation of the cyclic tetrapyrrole nucleus for the tetrapyrrole pigments (*J. Chem. Soc., Perkin Trans. 1*, 1996, 2079). The subsequent paper describes how they were able to use a combination of X-ray crystallography on a model system and CD correlation to determine the absolute stereochemistry of the active enantiomer of the spirocycle (*J. Chem. Soc., Perkin Trans. 1*, 1996, 2091). A whole issue of *Chem. Rev.* edited by B. E. Smart has been given over to fluorine chemistry, including extensive coverage of synthetic methodology (*Chem. Rev.*, 1996, *96*, 1555–1757).

As a tribute to Vladmir Prelog on his 90th birthday, issue 5 (1996) of *Helv. Chim. Acta* contains several dedicated articles including a discussion of the study of the origin of life by A. Eschenmoser and M. V. Kisakürek (*Helv. Chim. Acta*, 1996, *79*, 1249) and a review of how methods of evolution biology may be used to solve problems of synthetic chemistry by G. Quinkert and co-workers (*Helv. Chim. Acta*, 1996, *79*, 1260).

A unique mode of covalent catalysis by the B_6 dependent 1-aminocyclopropane-1-carboxylate (ACC) deaminase has recently been uncovered (K. Li *et al.*, *J. Am. Chem. Soc.*, 1996, *118*, 8763). The *exo*-methylene analogue **21** is a time dependent inhibitor of the enzyme, with **22** being the only product isolated, consistent with nucleophilic attack by an enzyme based nucleophile on the cyclopropane ring of the imine formed between B_6 and AAC. The deuteriated *exo*-methylene analogue **23** shows that nucleophilic attack must take place at C3 (**Scheme 2**).

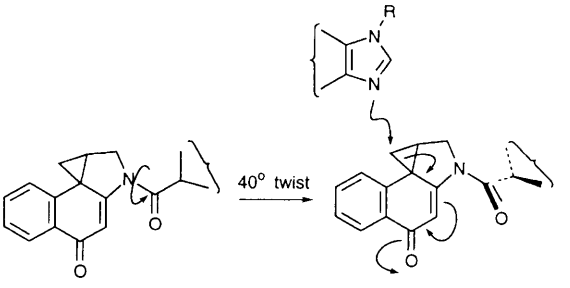


Scheme 2

The catalytic activities and the structure-function relationships of the enzymes of the cytochrome P450 group have been reviewed (B. A. Halkier, *Phytochemistry*, 1996, *43*, 1). J. B. Jones and co-workers have published a review discussing the need to expand the knowledge of 'enzyme–substrate interactions that regulate and control enzyme specificity' as a first step to allowing the reliable selection of the enzyme best suited to a particular chiral transformation (*Acta Chem. Scand.*, 1996, *50*, 697). This will allow accurate predictions of substrate suitability and rational mutagenesis for tailoring specificity.

The group of Mutter have reported the use of template assembled synthetic proteins (TASP) as functional protein mimics (*Angew. Chem., Int. Ed. Eng.*, 1996, *35*, 1482). The idea of peptide loops grafted onto a semi-rigid template (in this case a cyclic peptide) as a mimic of a protein active site or antibody combining site appears to be a realistic goal. Breslow and Still have used a **combinatorial approach to probe the specificity of binding of peptides to β-cyclodextrin** (*Angew. Chem., Int. Ed. Engl.*, 1996, *35*, 1490). A high selectivity for L-Phe-D-Pro and D-Phe-L-Pro was observed which was rationalized by NMR and molecular modelling studies. The generally accepted hydrogen bond accepting ability of fluorine has been called into question by O'Hagan's group (*Tetrahedron*, 1996, *52*, 12613). An evaluation of F···H contacts in the Cambridge Structural Database System showed very few C F···H–X short distance contacts, with C–F···H–C van der Waals contacts being more common. *Ab initio* calculations suggested that C(sp^3)–F forms stronger H-bonds than C(sp^2)–F, which is supported by the data in the structural database. A greater understanding of **the nature of the noncovalent interactions between proteins and ligands in solution and in the electrospray mass spectrometric gas phase** is emerging. C. V. Robinson *et al.* (*J. Am. Chem. Soc.*, 1996, *118*, 8646) have studied the protein–CoA ligand binding and assembly by both altering the length of the alkyl chain of the CoA and altering key residues on the protein. This shows that in the gas phase the requirements are different to the solution, with H-bond and π-stacking interactions being more important than hydrophobic interactions. Hydrogen–deuterium exchange experiments are also providing key evidence for the understanding of these interactions. The paper also includes some discussion of possible desolvation processes.

The concept of reactive immunisation for the generation of catalytic antibodies is discussed in a review by Learner and Barbas III (*Acta Chem. Scand.*, 1996, *50*, 672.). Immunization with a chemically reactive species that will undergo a reaction with the antibody results in that reaction becoming part of the mechanism of the catalytic event. This was then used to generate an antibody to catalyse an aldol condensation *via* an imine formed with the antibody. They describe the procedure as immunising with a 'reaction' rather than a 'molecule'. The subsequent paper discusses several issues related to the applicability of antibody-catalysed reactions to asymmetric synthesis (E. Keinan *et al.*, *Acta Chem. Scand.*, 1996, *50*, 679).



Scheme 3

An extensive review of the chemistry of the DNA alkylator CC1065 and an elegant elucidation of the mechanism of the sequence selectivity of the alkylation has been published by D. L. Boger and D. S. Johnson (*Angew. Chem., Int. Ed. Engl.*, 1996, *35*, 1438), clearly showing the relationship between structure, functional reactivity and biological properties. The trigger for the alkylation appears to be a twist induced in the linking amide bond leading to a more activated cyclopropyl ring (**Scheme 3**). A review of the various strategies for targeting RNA with conformationally restricted antisense agents has recently been published (P. Herdewijn, *Leibigs Ann.*, 1996, 1337). **The generally accepted mode of action of actinomycin by binding to double stranded DNA has been called into question** by R. M. Wadkins *et al.* (*J. Mol. Biol.*, 1996, *262*, 53). They present compelling evidence, both experimental and modelling, of actinomycin binding to single stranded DNA, which may be an important mode of binding for the inhibition of RNApol.