Chemoenzymatic and enantiodivergent routes to 1,2-ring-fused bicyclo[2.2.2]octane and related tricyclic frameworks†

Kerrie A. B. Austin, Jon D. Elsworth, Martin G. Banwell* and Anthony C. Willis

Received 19th October 2009, Accepted 17th November 2009
First published as an Advance Article on the web 7th December 2009
DOI: 10.1039/b921600f

New and simple protocols are described for the conversion of the enzymatically-derived and enantiomerically pure *cis*-1,2-dihydrocatechol 7 (X = I) and its 6-methylated derivative into either antipodal form of compounds embodying the tricyclic frameworks of terpenoids 1–6. Key steps include intramolecular Diels–Alder (IMDA) and (in some cases) singlet or triplet-based photochemical processes.

Bicyclo[2.2.2]octanes incorporating a 1,2-fused cyclopentane or cyclohexane ring are encountered in a number of interesting natural products.[1] For example, platencin (**1**), a structurally novel and potent anti-bacterial agent isolated from several strains of *Streptomyces platensis*, contains such a bicyclic framework that is fused to a cyclohexenone moiety.[2] The atisane,[1b,3] seco-atisane[4] and rhodolaurane[5]-type terpenoids also incorporate the same tricyclic ring system. On the other hand, 11-*O*-debenzoyltashironin (**2**), an anistatin-type natural product isolated from the Eastern Asian *Illicium merrillianum* and which promotes neurite outgrowth at concentrations as low as 0.1 μmol, embodies the cyclopent-annulated variant.[6] The latter ring system is also encountered in the khusiane,[7] eremolactone,[8] lacinane[9] and duprezianane[10] families of sesquiterpenoid or diterpenoid natural products. A representative member of the first of such families is (−)-khusiol (*allo*-cedrol) (**3**).[1c,11]

A further interest in the title frameworks derives from the potential of their bicyclo[2.2.2]oct-4-en-1-one derivatives to engage in various photochemically-promoted processes,[12] including decarbonylation, and thus presenting the possibility (*vide infra*) of obtaining the tricyclic ring systems associated with other terpenoids such as viridianol (**4**),[13] tamariscene (**5**)[14] and subergorgic acid (**6**).[15]

On the basis of the foregoing, we sought to develop efficient and flexible methods for obtaining 1,2-cyclopentannulated and 1,2-cyclohexannulated bicyclo[2.2.2]octanes in either enantiomeric form.[16] The key elements of our approach are shown in Fig. 1 and rely on the initial conversion of the enzymatically-derived and enantiomerically pure *cis*-1,2-hydrocatechols of the general form **7**[17] into the corresponding alkene-tethered system **8** (n = 1 or 2). The engagement of the latter systems in Type 1 intramolecular

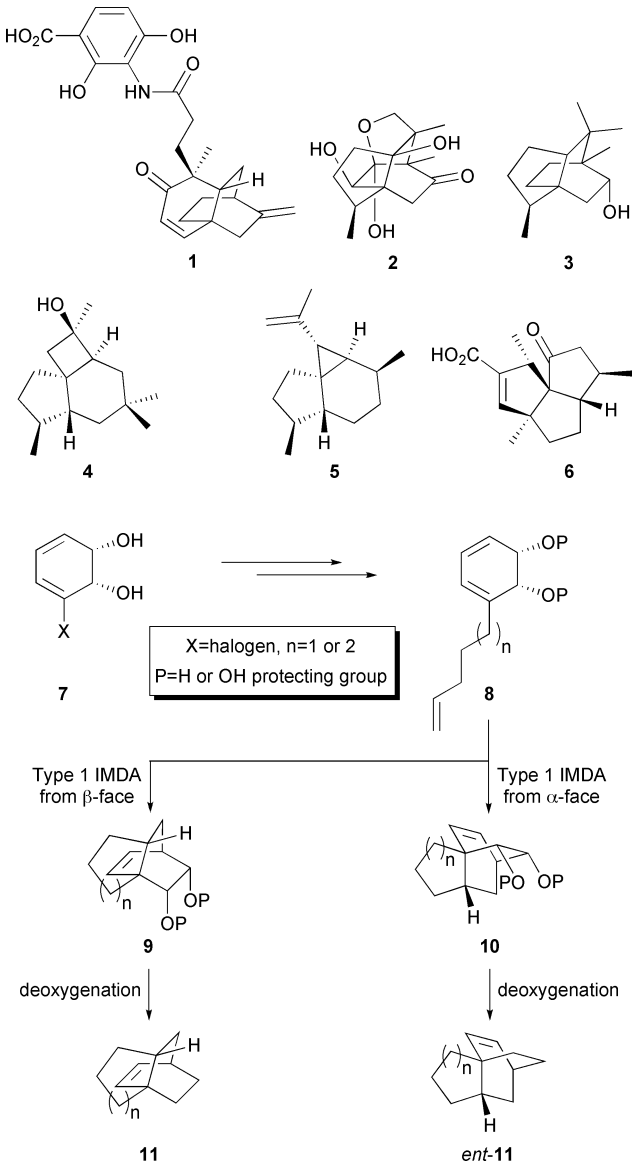


Fig. 1

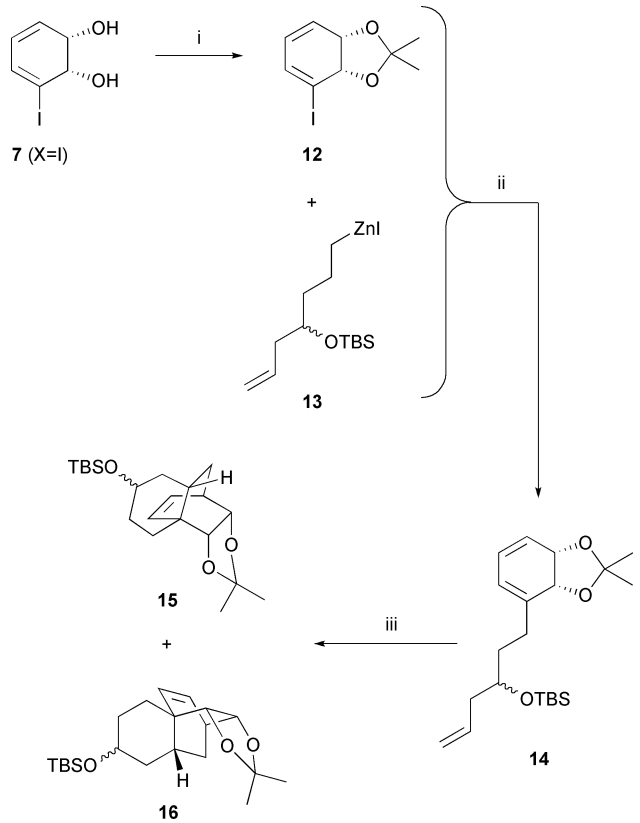
Diels–Alder (IMDA) cycloaddition reactions should then lead, *via endo*-type transition states, to adducts of the form **9** or **10** in which the former product arises from addition of the dienophile to the β-face of the diene while the latter involves the corresponding process taking place at the α-face.[18] The pseudo-enantiomeric relationship between products **9** and **10** is demonstrated by the fact that removal of the OP groups within each of these would lead to hydrocarbons **11** and *ent*-**11**, respectively. So, by controlling the

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia. E-mail: mgb@rsc.anu.edu.au

† Electronic supplementary information (ESI) available: Full experimental procedures; ^{1}H or ^{13}C NMR spectra of compounds **17**–**42**; data derived from single-crystal X-ray analyses of compounds **25**–**27**, **29**, **34** and **35**. CCDC reference numbers 747028 (for **25**), 747029 (for **26**), 747030 (for **27**), 747031 (for **29**), 747032 (for **34**), 750107 (for **35**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b921600f

facial selectivity of the IMDA process, either enantiomeric form of the target tricyclic framework could be obtained from a single enantiomeric form of the precursor *cis*-1,2-dihydrocatechol.

The details associated with the implementation of this basic strategy are provided in Schemes 1 and 2. Thus, as reported earlier,[19] the known and readily available acetonide derivative **12**[20] of diol **7** (X = I, Scheme 1) participated in a Negishi-type cross-coupling reaction with the organic zinc compound **13**[19] to give product **14** (65–85%) as a 1 : 1 mixture of diastereoisomers. Upon heating in refluxing toluene, compound **14** engaged in an *endo*-selective IMDA reaction to give a *ca.* 10 : 1 mixture of the β- and α-face addition products **15** and **16**, respectively, in 98% combined yield. The individual diastereoisomeric forms of these cycloadducts was each fully characterized by spectroscopic means including single-crystal X-ray diffraction analysis.[19] Compound



Scheme 1 *Reagents and conditions*: (i) $(MeO)_2CMe_2$, *p*-TsOH·H_2O (4 mole%), 18 °C, 1 h; (ii) $Pd(PPh_3)_4$ (10 mole%), THF, 18 °C, 3 h; (iii) BHT (3 mole%), toluene (reflux), 16 h.

15 embodies the natural enantiomeric form of the tricyclic hydrocarbon framework associated with platencin and has been used, by us, to establish a formal total synthesis of this natural product.[19] On the other hand, congener **16** embodies the non-natural enantiomeric form of the same target and efforts to elaborate this to *ent*-platencin (*ent*-**1**) are now underway in our laboratories.

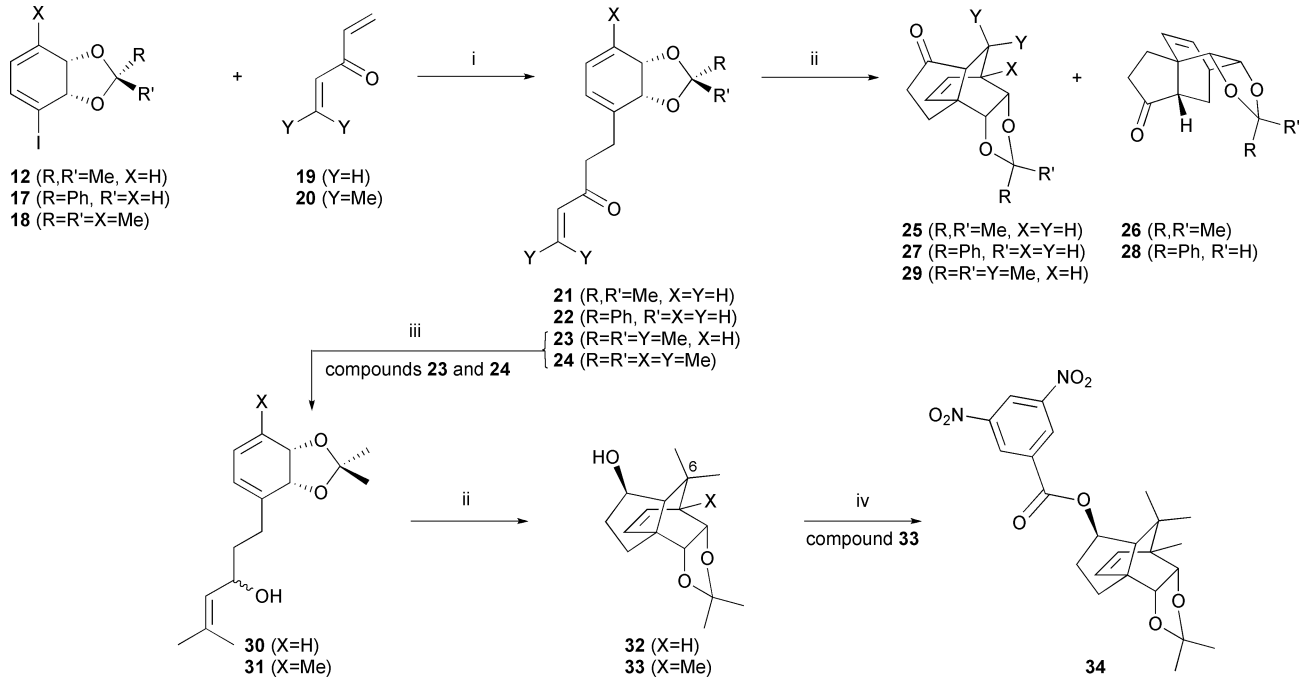
The early stages of the reaction sequences shown in Scheme 2 serve to highlight another method for tethering a dienophilic residue to the *cis*-1,2-dihydrocatechol core and so providing precursors to 1,2-cyclopentannulated bicyclo[2.2.2]octanes. Thus, treatment of the readily available acetal derivatives **12**, **17** and **18** of diol **7** (X = I) and its 6-methylated derivative[21] with isopropyl magnesium chloride then copper(I) bromide/dimethylsulfide complex followed by reaction of the ensuing cuprates with either of the readily prepared dialkenylketones **19**[22] or **20**[23] gave the expected conjugate addition products **21** (65%), **22** (63%), **23** (74%) or **24** (60%).[24] The first three of these products engaged in the anticipated IMDA reaction (Entries 1–3, Table 1). Thus, substrate **21** provided a near 1 : 1 mixture of the expected β- and α-face adducts **25**[25] (44%) and **26**[25] (39%), respectively, while congener **22** afforded a *ca.* 3 : 1 mixture of the analogous adducts **27** (59%) and **28** (21%). In contrast, the sole isolable product of reaction arising from thermolysis of substrate **23** was the β-face addition product **29**[25] (45%) and this was only generated upon heating the former compound in refluxing mesitylene for four days. Interestingly, the more heavily substituted substrate **24** failed to engage in the hoped-for IMDA reaction (Entry 4, Table 1) even under the forcing conditions defined immediately above for congener **23**.

The lack of reaction of compound **24** was disappointing because the hoped-for adducts would have incorporated the two contiguous quaternary carbon centres associated with the natural products **2** and **3**. This inertness might arise from conformational restrictions imposed upon substrate **24** by the side-chain carbonyl[26] and a consequent inability of the molecule to assume the transition state geometry required for the IMDA reaction. On this basis both compound **24** and congener **23** were subject to reduction with sodium borohydride and the resulting 1 : 1 mixtures of diastereoisomeric alcohols **30** (84%) and **31** (83%) were heated in mesitylene and by such means the adducts **32** (44%) and **33** (46%) were formed. Each of these adducts was obtained as a single diastereoisomer possessing the illustrated configuration of the free hydroxyl group on the newly formed five-membered ring. The structure of compound **33** was confirmed through a single-crystal X-ray analysis of the derived 3,5-dinitrobenzoate **34**.[25] The stereoselective formation of IMDA adducts **32** and **33** from an epimeric mixture of precursors is notable. Presumably

Table 1 Outcomes of the IMDA reactions of substrates **21–24**, **30** and **31**

Entry	Substrate	Reaction conditions	β-Adduct (%)	α-Adduct (%)
1	**21**	toluene, BHT[a], 112 °C, 16 h	**25** (44)	**26** (39)
2	**22**	toluene, BHT, 112 °C, 16 h	**27** (59)	**28** (21)
3	**23**	mesitylene, BHT, 165 °C, 96 h	**29** (45)	not observed
4	**24**	mesitylene, BHT, 165 °C, 96 h	no isolable product	no isolable product
5	**30**	mesitylene, BHT, 165 °C, 96 h	**32** (44)	not observed
6	**31**	mesitylene, BHT, 165 °C, 96 h	**33** (46)	not observed

[a] BHT = butylated hydroxytoluene (added as a free radical chain inhibitor).

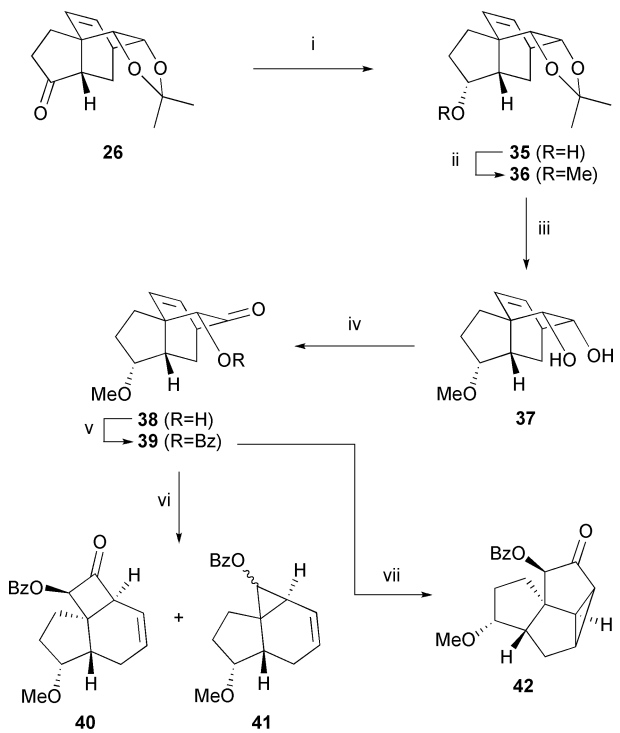


Scheme 2 *Reagents and conditions*: (i) *i*-PrMgCl (1.2 mole equiv.), THF, –30 to 0 °C, 2 h then cool to –78 °C, CuBr·SMe_2 (0.1 mole equiv.), HMPA (3.0 mole equiv.), TMS-Cl (3.0 mole equiv.), **19** or **20** (2.1 mole equiv.), 1.5 h then warm to 18 °C, 16 h; (ii) see Table 1; (iii) $NaBH_4$ (1.9 mole equiv.), methanol, 0 to 18 °C, 2 h; (iv) 3,5-$(O_2N)_2C_6H_3COCl$ (2.6 mole equiv.), Et_3N (3.5 mole equiv.), DMAP (3.5 mole equiv.), CH_2Cl_2, 18 °C, 16 h.

the transition states leading to the observed products are lower-lying in energy than those associated with their epimers because the hydroxyl groups and *endo*-orientated methyl group at C-6 are significantly further apart in the former case.

The capacity to manipulate the IMDA adducts described above is highlighted by the transformation of compound **26** shown in Scheme 3. Thus, as a prelude to conducting various photochemical conversions, adduct **26** was subjected to stereoselective reduction with L-selectride. *O*-Methylation of the resulting alcohol **35**[25] (87%) with methyl iodide in the presence of sodium hydride then gave the ether **36** (85%). Treatment of a methanol–water solution of the latter compound with acidic resin resulted in cleavage of the acetonide residue and formation of the diol **37** (77% at 90% conversion) that could be selectively oxidized to the acyloin **38** (84%) using the sterically demanding oxammonium salt derived from 4-(*N*-acetamido)-TEMPO and *p*-toluenesulfonic acid.[27] Following protocols we have applied to analogous 2,3-cyclopentannulated systems,[27] the readily derived *O*-benzoyl derivative **39** (99%) of compound **38** was subject to direct irradiation (in benzene at 300 nm using a Rayonet reactor). As a consequence, a 1,3-acyl-migration reaction[28] took place and thereby forming the cyclobutanone **40** (61%). This was accompanied by small amounts (16%) of the corresponding cyclopropane **41** that arises from a photochemically-promoted decarbonylation reaction of compound **40** (on sustained irradiation a pure sample of compound **40** was converted into cyclopropane **41** in 73% yield). In contrast, triplet-sensitised irradiation of substrate **39** resulted in an oxa-di-π-methane rearrangement[29] and formation of the expected tetracyclic compound **42** (54%). This product was accompanied by 8% of the previously observed cyclopropane **41**.

Since each of photoproducts **40–42** embody the tricyclic frameworks of the natural products **4–6**, respectively, or their



Scheme 3 *Reagents and conditions*: (i) L-selectride (2.0 mole equiv.), CH_2Cl_2, –78 °C, 1 h; (ii) MeI (3.0 mole equiv.), NaH (1.2 mole equiv.), THF, 20 °C, 18 h; (iii) activated DOWEX 50WX28-100 ion exchange resin, 5 : 1 v/v methanol–water, 110 °C, 72 h; (iv) 4-(NHAc)TEMPO (2.2 mole equiv.), *p*-TsOH·H_2O (2.2 mole equiv.), CH_2Cl_2, 0 to 20 °C, 3 h; (v) BzCl (3.0 mole equiv.), DMAP (4.0 mole equiv.), CH_2Cl_2, 0 to 20 °C, 20 h; (vi) irradiation at 300 nm, benzene, 20 °C, 2 h; (vii) irradiation at 300 nm, acetone, 20 °C, 10 h.

enantiomers, the protocols detailed here should be applicable to the preparation of these and other structurally related sesquiterpenoids. Work directed towards such ends is now underway in these laboratories. The capacity for enantiodivergent synthesis is also being refined by, *inter alia*, enhancing the α- or β-facial selectivity of the IMDA reactions described here through "tuning" of the groups used to protect the hydroxyl moieties within the *cis*-1,2-dihydrocatechol subunit of the relevant substrates.

Notes and references

1 See, for example: (*a*) T. K. Devon and A. I. Scott, *Handbook of Naturally Occurring Compounds – Volume II: Terpenes*, Academic Press, New York, 1972; (*b*) P. S. Shanker and G. S. R. Subba Rao, *J. Chem. Soc., Perkin Trans. 1*, 1998, 539; (*c*) B. M. Fraga, *Nat. Prod. Rep.*, 2009, **26**, 1125 and earlier reviews in the series.

2 (*a*) J. Wang, S. Kodali, S. H. Lee, A. Galgoci, R. Painter, K. Dorso, F. Racine, M. Motyl, L. Hernandez, E. Tinney, S. L. Colletti, K. Herath, R. Cummings, O. Salazar, I. González, A. Basilio, F. Vicente, O. Genilloud, F. Pelaez, H. Jayasuriya, K. Young, D. F. Cully and S. B. Singh, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 7612; (*b*) H. Jayasuriya, K. B. Herath, C. Zhang, D. L. Zink, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, I. Gonzalez, O. Salazar, F. Pelaez, R. Cummings, S. Ha, J. Wang and S. B. Singh, *Angew. Chem., Int. Ed.*, 2007, **46**, 4684.

3 For examples of a recently isolated members of this family see (*a*) N. B. Perry, E. J. Burgess, S.-H. Baek and R. T. Weavers, *Org. Lett.*, 2001, **3**, 4243; (*b*) T. Kume, N. Asai, H. Nishikawa, N. Mano, T. Terauchi, R. Taguchi, H. Shirakawa, F. Osakada, H. Mori, N. Asakawa, M. Yonaga, Y. Nishizawa, H. Sugimoto, S. Shimohama, H. Katsuki, S. Kaneko and A. Akaike, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 3288.

4 See, for example, J.-D. Wang, Z.-Y. Li, W.-S. Xiang and Y.-W. Guo, *Helv. Chim. Acta*, 2006, **89**, 1367 and references cited therein.

5 See, for, example, A. G. González, J. D. Martín, V. S. Martín, R. Pérez, B. Tagle and J. Clardy, *J. Chem. Soc., Chem. Commun.*, 1985, 260.

6 See S. P. Cook, A. Polara and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2006, **128**, 16440 and references cited therein.

7 See, for example, (*a*) R. N. Ganguly, G. K. Trivedi and S. C. Bhattacharyya, *Indian J. Chem., Sect. B*, 1978, **16**, 23; (*b*) P. Weyerstahl, H. Marschall and C. Christiansen, *Flavour Fragrance J.*, 2001, **16**, 50; (*c*) Y. O. Nuñez, I. S. Salabarria, I. G. Collado and R. Hernández-Galán, *Phytochemistry*, 2007, **68**, 2409.

8 See, for example, (*a*) R. Ramage, O. J. R. Owen and I. A. Southwell, *Tetrahedron Lett.*, 1983, **24**, 4487; (*b*) M. Asaoka, K. Ishibashi, N. Yanagida and H. Takei, *Tetrahedron Lett.*, 1983, **24**, 5127 and references cited therein.

9 See, for example, Y. Fukushi, C. Yajima, J. Mizutani and S. Tahara, *Phytochemistry*, 1998, **49**, 593.

10 See, for example, A. F. Barrero, J. Quílez del Moral and A. Lara, *Tetrahedron*, 2000, **56**, 3717 and referencescited therein.

11 B. Tomita and Y. Hirose, *Phytochemistry*, 1973, **12**, 1409.

12 See (*a*) V. Singh, G. D. Praveena, K. Karki and S. M. Mobin, *J. Org. Chem.*, 2007, **72**, 2058 and references cited therein; (*b*) V. Singh, R. B. Singh and S. M. Mobin, *Tetrahedron*, 2009, **65**, 7969.

13 M. Norte, J. J. Fernández and M. L. Souto, *Tetrahedron Lett.*, 1994, **35**, 4607.

14 C. Paul, W. A. König and H. Muhle, *Phytochemistry*, 2001, **57**, 307.

15 See J. C. Gilbert and J. Yin, *Tetrahedron*, 2008, **64**, 5482 and references cited therein.

16 For a description of a recent and distinct approach to the racemic modifications of the title ring systems see V. Singh, P. K. Sahu, B. C. Sahu and S. M. Mobin, *J. Org. Chem.*, 2009, **74**, 6092.

17 Compound **7** (X = I) can be obtained from Questor, Queen's University Belfast, Northern Ireland. Questor Centre Contact Page: http://questor.qub.ac.uk/newsite/contact.htm (accessed October 7, 2009). For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see: (*a*) T. Hudlicky, D. Gonzalez and D. T. Gibson, *Aldrichimica Acta*, 1999, **32**, 35; (*b*) M. G. Banwell, A. J. Edwards, G. J. Harfoot, K. A. Jolliffe, M. D. McLeod, K. J. McRae, S. G. Stewart and M. Vögtle, *Pure Appl. Chem.*, 2003, **75**, 223; (*c*) R. A. Johnson, *Org. React.*, 2004, **63**, 117; (*d*) T. Hudlicky and J. W. Reed, *Synlett*, 2009, 685.

18 Intermolecular and α-face selective Diels–Alder reactions of *cis*-1,2-dihydrocatechols have been reported previously: J. R. Gillard and D. J. Burnell, *J. Chem Soc., Chem. Commun.*, 1989, 1439.

19 K. A. B. Austin, M. G. Banwell and A. C. Willis, *Org. Lett.*, 2008, **10**, 4465.

20 D. R. Boyd, N. D. Sharma, N. M. Llamas, J. F. Malone, C. R. O'Dowd and C. C. R. Allen, *Org. Biomol. Chem*, 2005, **3**, 1953.

21 C. C. R. Allen, D. R. Boyd, H. Dalton, N. D. Sharma, I. Brannigan, N. A. Kerley, G. N. Sheldrake and S. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1995, 117.

22 Compound **19** was prepared using a modification of the procedure of Reed (S. F. Reed, *J. Org. Chem.*, 1962, **27**, 4116) wherein DDQ rather than MnO_2 was used to effect oxidation of the intermediate divinylcarbinol.

23 Compound **20** was prepared according to the method of Mironov *et al.* (G. S. Mironov, M. I. Farberov and I. M. Orlova, *Russ. J. Gen. Chem.*, 1963, **33**, 1476).

24 For examples of related conjugate addition reactions see (*a*) Y. Horiguchi, S. Matsuzawa, E. Nakamura and I. Kuwajima, *Tetrahedron Lett.*, 1986, **27**, 4025; (*b*) J.-F. Brière, R. H. Blaauw, J. C. J. Benningshof, A. E. van Ginkel, J. H. van Maarseveen and H. Hiemstra, *Eur. J. Org. Chem.*, 2001, 2371.

25 This compound has been subject to single-crystal X-ray analysis and the details deposited with the Cambridge Crystallographic Data Centre (CCDC). Deposition numbers are: 747028 (for **25**), 747029 (for **26**), 747030 (for **27**), 747031 (for **29**), 747032 (for **34**), 750107 (for **35**).

26 Similar restrictions have been noted in related systems: M. D. Mihovilovic, H. G. Leisch and K. Mereiter, *Tetrahedron Lett.*, 2004, **45**, 7087.

27 For an example of a related oxidationsee: M. G. Banwell, K. A. B. Austin and A. C. Willis, *Tetrahedron*, 2007, **63**, 6388. This protocol is based on one first described by Ma and Bobbitt; (Z. Ma and J. Bobbitt, *J. Org. Chem.*, 1991, **56**, 6110).

28 R. S. Givens and W. F. Oettle, *J. Am. Chem. Soc.*, 1971, **93**, 3963.

29 Demuth has highlighted the utility of the oxa-di-π-methane rearrangement in constructing both linear and angular triquinane frameworks (M. Demuth and W. Hinsken, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 973).

