

New methods for the synthesis of certain alkaloids and terpenoids*

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Abstract: The use of ring-fused *gem*-dihalocyclopropanes, Au(I)-catalyzed cyclization reactions, and chemoenzymatic techniques in the synthesis of natural products is described.

Keywords: chemoenzymatic techniques; *gem*-dihalocyclopropanes; gold-catalyzed reactions; natural products; organic synthesis.

INTRODUCTION

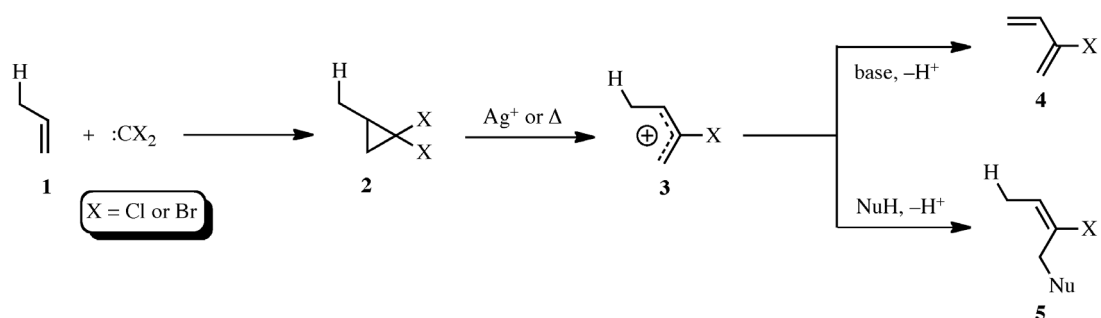
The total synthesis of natural products continues to represent an important and challenging activity that is undertaken for a variety of reasons. Pivotal among these is the need to prove chemical structure and/or the need to obtain sufficient quantities of material for comprehensive biological evaluation. Of course, the structurally novel features of many natural products often provide the inspiration for the development of new methodologies and strategies [1]. Herein, we describe some of our group's activities in the area that involve the application of three distinct protocols for facilitating natural products synthesis, namely the use of *gem*-dihalocyclopropanes as chemical building blocks, Au(I)-catalyzed cyclization reactions, and chemoenzymatic methodologies. These are discussed separately in the following sections.

***gem*-DIHALOCYCLOPROPANES AS BUILDING BLOCKS IN NATURAL PRODUCTS SYNTHESIS**

gem-Dichloro- and *gem*-dibromocyclopropanes (**2**) are readily obtained through addition of the relevant dihalocarbene to the corresponding alkene **1** (Scheme 1). The most effective protocols for achieving these additions involve those developed by Makosza and Brinker [2]. Specifically, a solution of the alkene **1** in chloroform or bromoform containing a phase-transfer catalyst, often a quaternary ammonium salt such as triethylbenzylammonium chloride (TEBAC), is treated with 50 % aqueous sodium hydroxide and the resulting two-phase system is stirred vigorously (or sonicated), normally at or near room temperature. While these conditions might appear to be especially vigorous ones, in fact the hydroxide ion concentration in the organic phase is very low and such that the carbon–carbon double bond of allylic acetates, for example, can be successfully cyclopropanated without any accompanying saponification of the ester unit [3].

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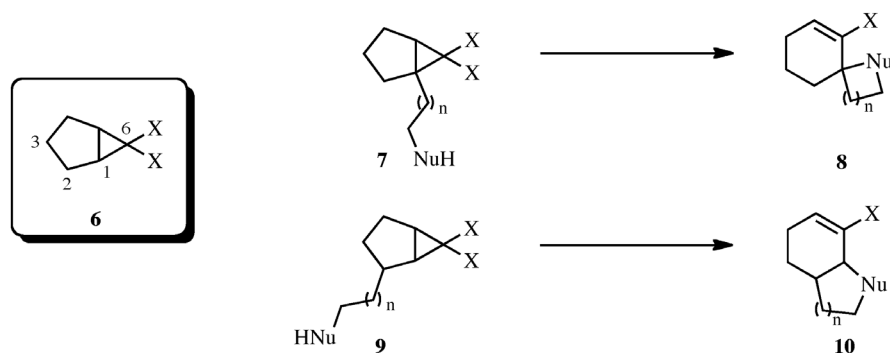


Scheme 1

An important feature of *gem*-dihalocyclopropanes (**2**) is that while they are strained organic molecules they also possess a remarkable kinetic stability. Indeed, the reactivity of these systems is orthogonal to most other functional groups and such that they can be carried through multi-step reaction sequences with impunity. Yet, at the appointed time, and by treating the *gem*-dihalocyclopropane with a silver salt or (less preferably) by heating it, electrocyclic ring-opening of the three-membered ring can be effected and thereby generating the corresponding π -allyl cation **3** [3]. The precise fate of this intermediate depends upon the conditions under which it is produced. When a basic environment is involved, then deprotonation of cation **3** occurs and 2-halo-1,3-butadienes of the general form **4** are obtained. Alternatively, a range of nucleophiles (NuH) can be added to the reaction mixture so as to intercept cation **3** and allylic systems such as **5** are thereby formed. When unsymmetrical cations are generated, then mixtures of regioisomeric trapping products are often encountered in cases where external nucleophiles are used to intercept such species. In contrast, and as illustrated below, intramolecular nucleophilic trapping is normally a completely regioselective process [3].

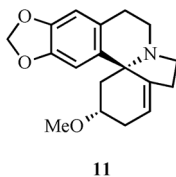
It is noteworthy that the reaction sequence $1 \rightarrow 2 \rightarrow 5$ results in the conversion of a mono-functional starting material into a tri-functional product. As such, there is a strong “value-adding” aspect to the sequence that is further reinforced by the capacity to engage the alkenyl halide substructure within compound **5** in palladium-catalyzed cross-coupling reactions and thereby replacing the halogen with carbon-based groups (of course, the same cross-coupling processes can be applied to halodiene **4**). Another interesting feature of this reaction sequence is the capacity it provides for the stereocontrolled synthesis of tri- and tetra-substituted carbon–carbon double bonds, something that is often difficult to achieve by more conventional means.

A subset of *gem*-dihalocyclopropanes of particular interest to us are those systems arising from dihalocarbene addition to cyclopentenenes. This is because these bicyclo[3.1.0]hexanes (**6**) lead, upon electrocyclic ring opening, to functionalized and synthetically valuable cyclohexenes. Such processes are facilitated by the extra strain incorporated within these ring-fused systems. Furthermore, within the bicyclo[3.1.0]hexane framework there are four distinct positions, at C1, C2, C3, and C6, where tethered nucleophiles can be introduced and thereby allowing for the trapping of the derived π -allyl cation in an intramolecular fashion (Scheme 2). Thus, for example, reaction of the C1 tethered system **7** should provide a spirocyclic product of the form **8** while the analogous C2 tethered system **9** should lead to the ring-fused system **10**. In each instance, the tethered nucleophile would be expected, on kinetic grounds, to attack the proximate rather than the remote terminus of the intermediate π -allyl cation.

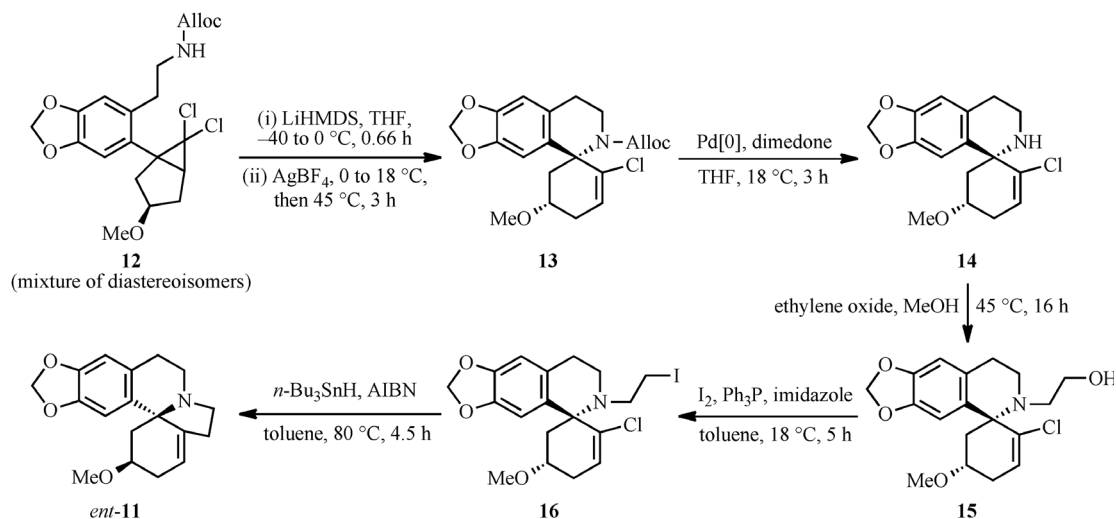


Scheme 2

The utility of the first of these processes described above has been demonstrated during the course of our synthesis of the non-natural or (+)-enantiomeric form of the erythrina alkaloid (–)-erythramine (**11**) [4].

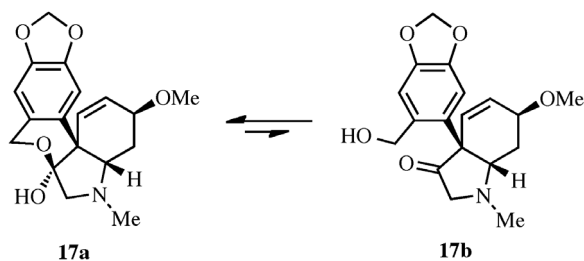


The key substrate used in the synthesis was the *gem*-dichlorocyclopropane **12** (Scheme 3) which could be prepared, as a mixture of diastereoisomers, through the addition of dichlorocarbene to the corresponding alkene [4]. This alkene was itself generated through Suzuki–Miyaura cross-coupling of the corresponding and enantiomerically pure cyclopentenyl triflate to the relevant arylboronic acid. The pivotal spirocyclization event was carried out by first treating compound **12** with LiHMDS, to deprotonate at nitrogen, and then reacting the resulting conjugate base with silver tetrafluoroborate. By such means, a chromatographically separable mixture of compound **13** (30 %) and its C5 epimer (26 %) was obtained. The completion of the synthesis required establishment of an ethylene bridge between nitrogen and sp^2 -hybridized carbon bearing the chlorine in product **13**. In our first attempts to effect this conversion, compound **13** was treated with various alkyl lithiums in an effort to metallate the halogenated carbon and then react this with, for example, ethylene oxide. However, despite extensive experimentation, all efforts to replace the chlorine in compound **13** with anything other than hydrogen failed. Accordingly, the illustrated means for completing the synthesis was established. Thus, compound **13** was treated with Pd[0] and dimedone so as to remove the Alloc-protecting group at nitrogen and the resulting 2°-amine **14** (90 %) was then treated with ethylene oxide to afford the hydroxy-amine **15** (60 %), the structure of which was confirmed by single-crystal X-ray analysis. Alcohol **15** was then converted into the corresponding iodide **16** under standard conditions. Treatment of this iodide with *n*-Bu₃SnH resulted in homolysis of the C–I bond and the ensuing 1°-radical engaged in a 5-exo-trig cyclization reaction and the 2°-radical so-formed then collapsed with ejection of a chlorine radical so as to re-establish the carbon–carbon double bond with complete positional fidelity and thereby completing the synthesis of (+)-erythramine [(+)-**11**] (89 % from **15**) [4].

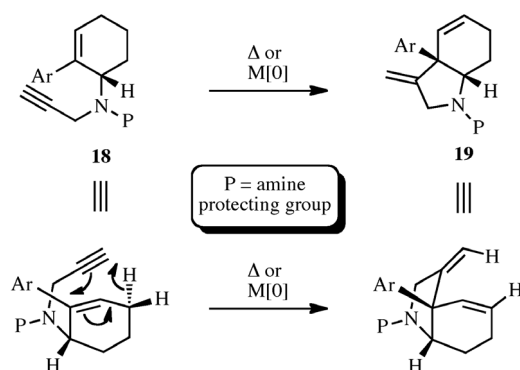


Scheme 3

Another alkaloid of interest to us is the lactol-containing compound tazettine (**17**) [5] which, especially when considered in its ring-opened form **17b**, quite clearly embodies a C3a-arylhexahydroindole unit. Because this motif is encountered in numerous other *Amaryllidaceae* alkaloids, various methods for its construction have been investigated [6].

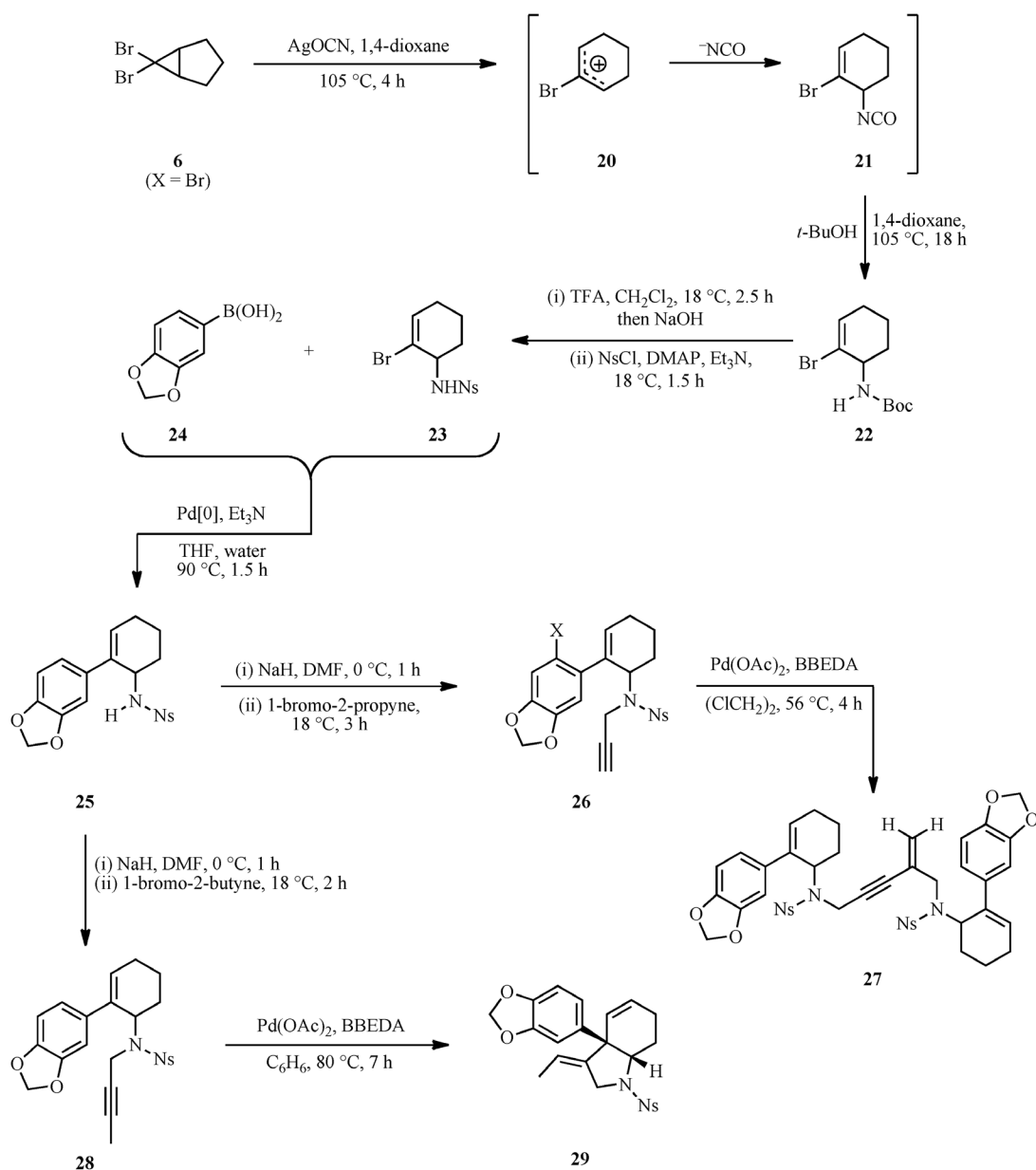


The plan we adopted for preparing this unit is shown in Scheme 4 and involved engaging the *N*-protected and propargylated 1-amino-2-aryl-2-cyclohexenes of the general form **18** in an intramolecular Alder-ene (IMAE) reaction thus producing a C3a-arylhexahydroindole **19** incorporating the required Δ^4 -double bond as well as an exocyclic one at C3 [7]. Provided the latter alkene could be oxidatively cleaved in a selective manner, this moiety should serve as a precursor to a carbonyl or hydroxyl group often encountered at C3 in the above-mentioned natural products. Clearly, the utility of such a process, if viable, would depend upon how readily or otherwise the substrates for the IMAE reaction could be synthesized.



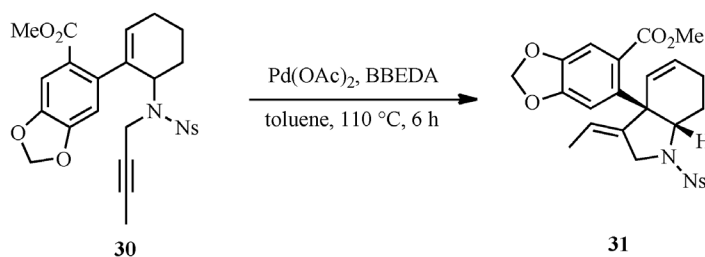
Scheme 4

Our synthesis of the required *N*-protected and propargylated 1-amino-2-aryl-2-cyclohexenes is shown in Scheme 5 and involves a silver cyanate-induced electrocyclic ring opening of the readily available *gem*-dibromocyclopropane **6** ($X = \text{Br}$) and trapping of the intermediate π -allyl cation **20** with cyanate ion [7]. The resulting allylic isocyanate **21** is itself trapped with added *t*-butanol, thus affording the isolable Boc-protected allylic amine **22** in 75 % yield. Since carbamate-protected amines are likely to prevent the target substrates **18** from adopting the geometry required for the IMAE reaction, the Boc-group within compound **22** was cleaved using TMSOTf in the presence of 2,6-lutidine or with trifluoroacetic acid (TFA) alone and the resulting 1°-amine treated with *o*-nitrobenzenesulfonyl chloride (NsCl) and thereby affording nosylate **23** (73 % from **22**). The sulfonamide-based protecting group was chosen because of the likelihood of the associated nitrogen being able to assume a geometry that would allow for the desired cyclization reaction. The nosyl protecting group was also considered a particularly attractive one because of the ease with which it can be removed using the phenylthiolate anion. Suzuki–Miyaura cross-coupling of 3,4-methylenedioxyphenyl boronic acid (**24**) with cyclohexenyl bromide **23** resulted in the formation of the 1-amino-2-aryl-2-cyclohexene **25** (69 %) which was treated, successively, with sodium hydride then propargyl bromide to afford the first substrate, **26** (89 %), required to investigate the proposed IMAE reaction. In the event, subjecting this compound to reaction with $\text{Pd}(\text{OAc})_2$ and the strong donor ligand bis(benzylidene)ethylenediamine (BBEDA) in refluxing benzene, conditions known to effect ene reactions in other systems, only resulted in the dimerization of the substrate to give compound **27** as a ca. 1:1 mixture of diastereoisomers. In order to prevent this unwanted process, the methyl-capped substrate **28** was prepared by straightforward means and subjected to the same reaction conditions. Gratifyingly, the desired C3a-arylhexahydroindole **29** was now formed in 94 % yield and its structure confirmed by single-crystal X-ray analysis.



Scheme 5

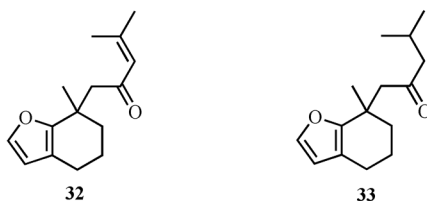
Substrate **30** (Scheme 6), incorporating a carbomethoxy group that could be used to establish the lactol unit of tazettine, also participates in the desired IMAE reaction to give compound **31** in 55 % yield. Efforts to exploit such reaction sequences in establishing an abbreviated and enantioselective synthesis of natural product **17** are now underway.



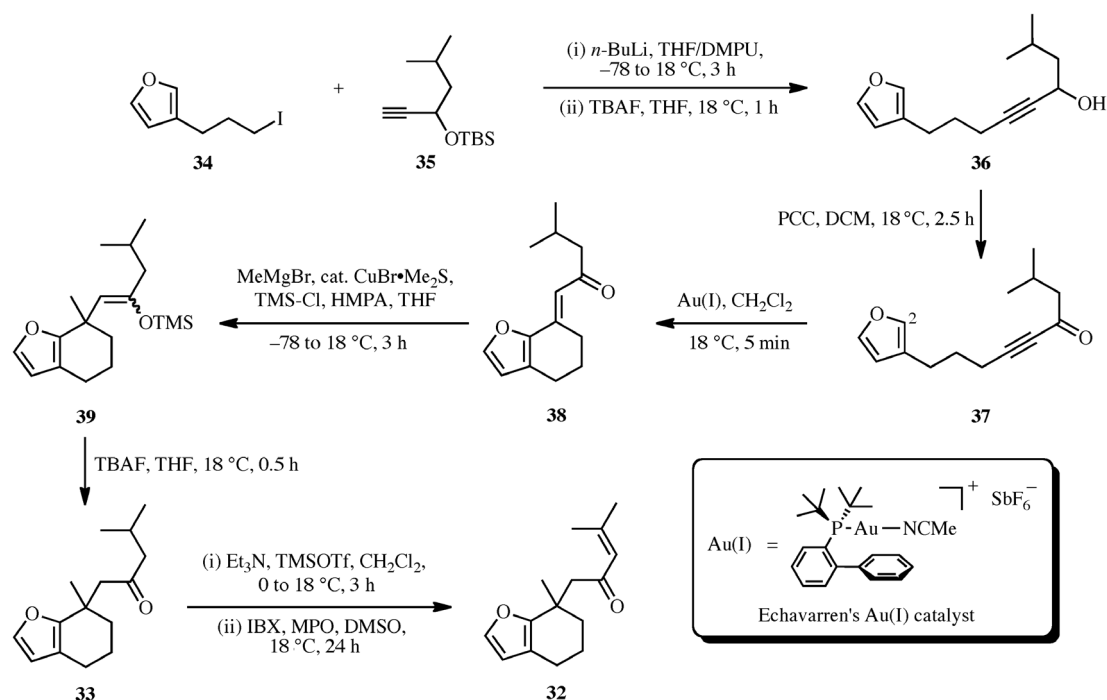
Scheme 6

NEW GOLD(I)-CATALYZED PROCESSES FOR NATURAL PRODUCTS SYNTHESIS

Gold-catalyzed processes are attracting increasing attention in natural products synthesis, not least because of the novel and selective transformations such species can promote, and often under very mild conditions [8]. Our interest in the area arose when we discovered that the highly versatile and now commercially available Au(I) catalyst developed by Echavarren (*vide infra*) can effect the intramolecular hydroarylation (IMHA) of a significant range of acetylenic ethers, esters, and amines, thus affording, for example, coumarins, benzofurans, or dihydroquinolines [9]. As an extension of such work, we have been investigating other reactions that this catalyst is capable of effecting and have now discovered that it can promote intramolecular Michael additions of certain nucleophilic heterocycles to tethered ynone. This process is best illustrated in connection with our very recent development of the first total syntheses [10] of the furanosesquiterpenes crassifolone (**32**) and dihydrocrassifolone (**33**) [11].



The reaction sequence starts (Scheme 7) with the base-promoted coupling of the furan-substituted iodopropane **34** with the terminal acetylene **35** and treatment of the ensuing product with tetra-*n*-butylammonium fluoride (TBAF) to give the alcohol **36** (76 % over two steps). Oxidation of the last compound with pyridinium chlorochromate (PCC) then afforded the ynone **37** (90 %) that we anticipated would engage in an acid-catalyzed intramolecular Michael addition reaction whereby the nucleophilic C2 of the furan residue attacks at the proximate *sp*-hybridized carbon and so forming the six-membered ring required in assembling the bicyclic framework of targets **32** and **33**. In the event, all efforts to effect this transformation of substrate **37** using any one of a range of protic or Lewis acids failed. In stark contrast, treatment of a dichloromethane solution of the same compound with 1 mol % of the Echavarren's catalyst at room temperature resulted in the quantitative formation, after just 15 minutes, of the desired furannulated cyclohexane **38**. We speculate that this remarkable transformation involves initial auration at C2 of the substrate [12] and that this is followed by intramolecular Michael addition of this now highly nucleophilic center to the sterically uncongested β -terminus of the tethered ynone. Protio-deauration would then give compound **38**, which is obtained as a single geometric isomer (and tentatively assigned as possessing the illustrated *E*-configuration).

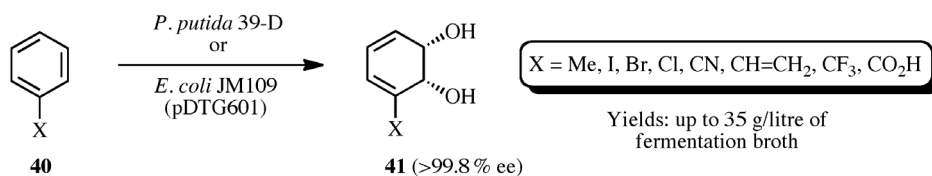


Scheme 7

The elaboration of compound **38** to crassifolone and dihydro-analogue **33** involved its reaction with methyl magnesium bromide in the presence of stoichiometric quantities of trimethylsilyl chloride and catalytic quantities of the cuprous bromide/dimethyl sulfide complex. The ensuing silyl enol ether **39** (66 %) was treated with TBAF and dihydrocrassifolone (**33**) thereby obtained in 61 % yield. Compound **33** could be converted into congener **32** (96 % at 50 % conversion) by successive treatment with TMSOTf in the presence of triethylamine then IBX in the presence of MPO. The spectral data obtained on each of the synthetically derived compounds **32** and **33** matched those reported [11] for the corresponding natural product.

CHEMOENZYMATIC METHODS IN NATURAL PRODUCTS SYNTHESIS

The whole-cell biotransformation of arenes **40** using genetically engineered organisms such as *P. putida* 39-D or *E. coli* JM 109 (pDTG601) that over-express the enzyme toluene dioxygenase (TDO) or related species allows, in optimal circumstances, for the formation of the corresponding *cis*-1,2-dihydrocatechol **41** in high chemical yield and >99.8 % enantiomeric excess (Scheme 8) [13]. Given this and the capacity to selectively manipulate the strongly differentiated functionality within compound **41**, such species can be considered as useful new chemical feedstocks for the synthesis of a wide range of target compounds. Like others, we have become interested in using these metabolites as starting materials for the synthesis of various natural products and other biologically active compounds [14].



Scheme 8

Some indication of the diversity of structures that can be obtained through chemical manipulation of the *cis*-1,2-dihydrocatechols is highlighted in Fig. 1 which shows a range of target compounds our group has prepared from these starting materials in recent years [15].

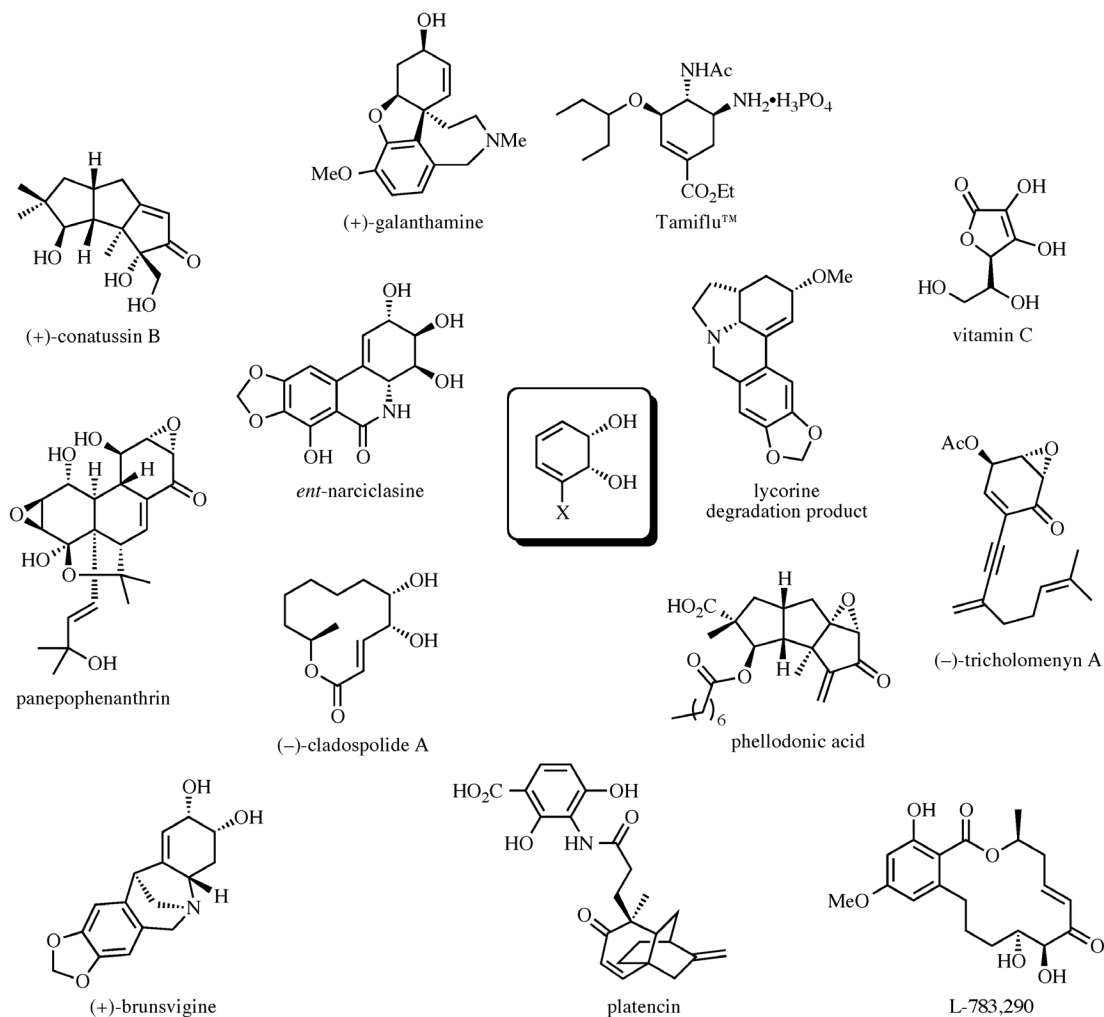
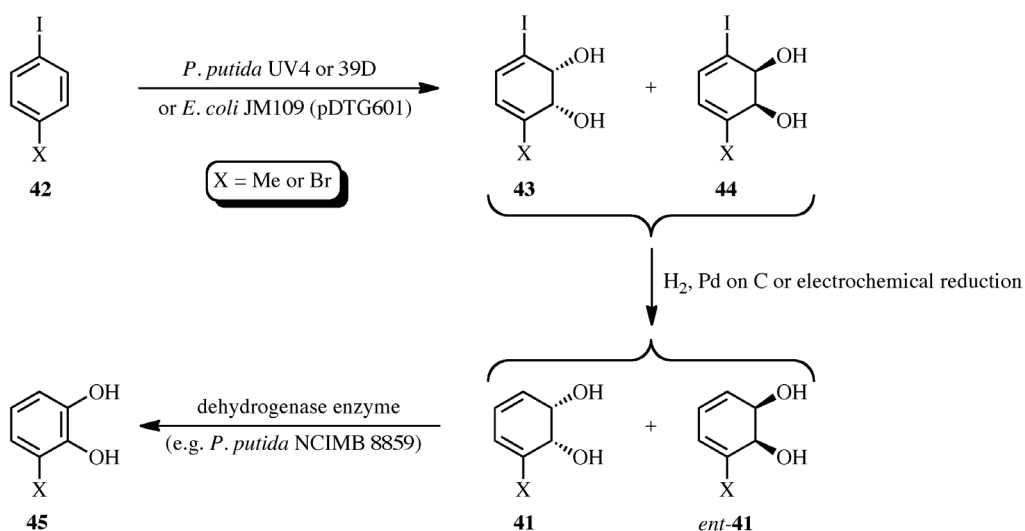


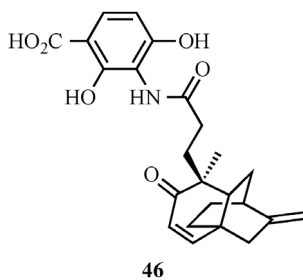
Fig. 1

Of course, one of the challenges associated with using the above-mentioned *cis*-1,2-dihydrocatechols in synthesis arises when there is a mismatch between the chirality of the starting material and the target compound. While the enantiomeric enzyme, i.e., *ent*-TDO, is unlikely to be accessible there are chemical means for obtaining the opposite enantiomeric form of certain of the *cis*-1,2-dihydrocatechols. Thus, for example, Boyd and his colleagues have demonstrated [16] that when TDO acts on the *p*-iodinated equivalent, **42**, of arene **40**, then (Scheme 9) a ca. 1:9 mixture of the enantiomeric diols **43** and **44** is obtained. Reductive deiodination of these metabolites, which can be achieved electrochemically or by Pd-catalyzed hydrogenolysis, affords the corresponding mixture of compounds **41** and *ent*-**41**. Treatment of this mixture with certain organisms that express dehydrogenase enzymes results in the selective aromatization of compound **45** to give catechol **46**, which can be separated chromatographically from the unaffected metabolite *ent*-**41** that is thus obtained in essentially enantiomerically pure form.

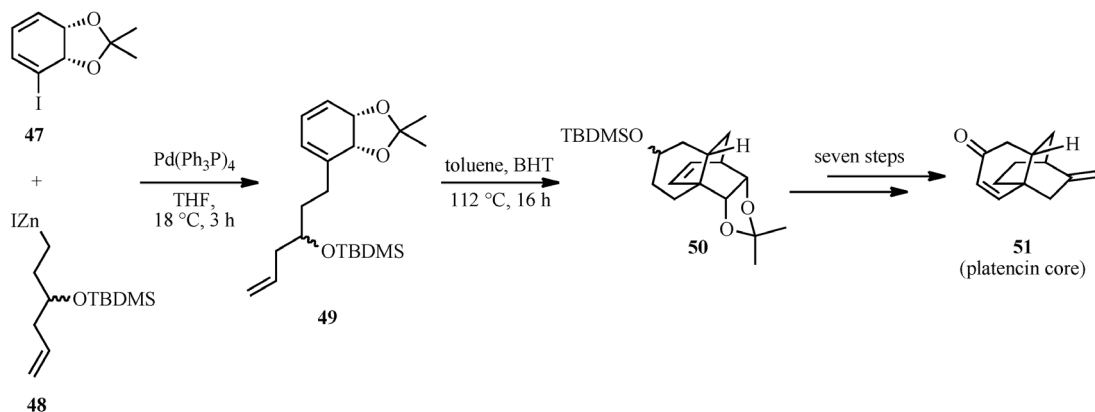


Scheme 9

In a related vein, we have uncovered enantiomeric switching regimes that allow, in certain circumstances, for the conversion of *cis*-1,2-dihydrocatechol **41** into either enantiomeric form of various derivatives. A useful example of such a regime arose during the course of our recently reported [15e] synthesis of the tricyclic core of the novel antibacterial agent platencin (**46**), a natural product isolated by Singh and co-workers from *Streptomyces platensis* MA7327 [17].

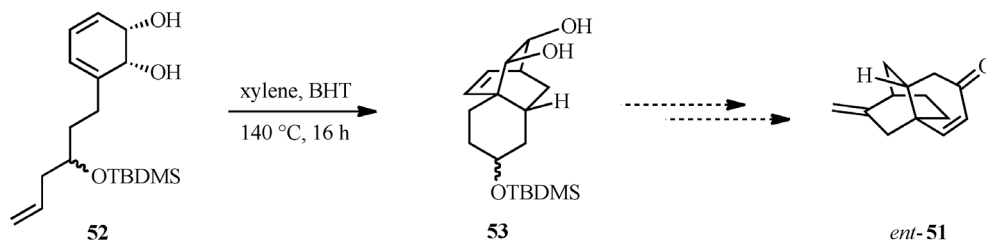


Our approach to this significant compound is shown in Scheme 10 and starts with the conversion of the iodobenzene-derived *cis*-1,2-dihydrocatechol **41** ($X = I$) into the corresponding acetonide **47** (91 %) under standard conditions. The latter compound was then subjected to a Negishi cross-coupling with the organozinc species **48**. The triene **49** (62 %) thus obtained was heated in refluxing toluene (in the presence of the free-radical inhibitor BHT) and thereby effecting a highly selective intramolecular Diels–Alder (IMDA) reaction leading to adduct **50** (89 %) embodying the tricyclic framework of platencin. A further seven and relatively conventional steps were then used to convert the latter compound into enone **51**, the key intermediate associated with the Nicolaou and Rawal total syntheses of platencin [18].



Scheme 10

It also seems possible to obtain the enantiomer of enone **51** (i.e., *ent*-**51**) from the same *cis*-1,2-dihydrocatechol, namely, compound **41** ($X = I$). Thus, the triene **52** (Scheme 11), which was readily generated employing chemistry similar to that used to obtain the acetonide-protected variant **49**, engages in an IMDA reaction upon heating in refluxing xylene, but now this process involves addition of the dienophile to the same face of the diene as occupied by the hydroxyl groups and thereby affords adduct **53** (55 %). The precise origins of the facial selectivity associated with this cycloaddition process remain unclear but they are presumably related to a stabilizing interaction between the dienophilic double bond and the hydroxyl groups. The pseudo-enantiomeric relationship between compound **53** and adduct **50** is emphasized by the expectation that chemistry analogous to that used in the conversion $\text{50} \rightarrow \text{51}$ would lead to compound *ent*-**51**, the core of *ent*-platencin (*ent*-**48**).



Scheme 11

Related enantiomeric switching regimes involving IMDA processes wherein the dienophile is attached, through ester linkages, to one or other of the hydroxyl groups of the *cis*-1,2-dihydrocatechols have also been developed by us [19]. As such, and given the wide range of structurally diverse natural products that can be prepared from the *cis*-1,2-dihydrocatechols (see Fig. 1) we anticipate that these compounds will continue to play an important role in chemical synthesis for some time to come.

ACKNOWLEDGMENTS

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