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Application of intramolecular Heck reactions for forming congested Quaternary carbon centers in complex molecule total synthesis

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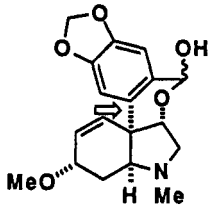
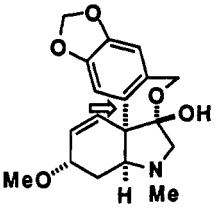
Abstract. Palladium-catalyzed cyclizations of aryl halides, vinyl halides and vinyl triflates with tethered alkenes have proven to be powerful reactions for forging congested quaternary carbon centers in complex organic molecules. In some cases, the use of enantiopure ligands allows the new quaternary center to be formed with excellent enantioselectivity. The scope, stereochemical nuances and power of this organometallic chemistry is illustrated by briefly considering our recent total syntheses of (±)-pretazettine, (±)-tazettine, (-)- and (+)-morphine, (-)- and (+)-physostigmine, (±)-scopadulcic acid A and (±)-scopadulcic acid B.

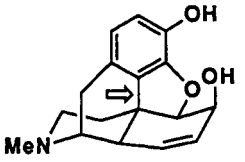
Reactions of organopalladium halides, triflates and similar intermediates lacking β-sp^3-bonded hydrogens with unhindered alkenes are among the most versatile methods for preparing complex alkenes (ref. 1). The recent extraordinary growth in the use of this chemistry (often called the Heck reaction) in both industrial and academic organic synthesis is largely attributable to the excellent functional group tolerance of palladium-catalyzed reactions. A wide variety of aromatic and vinylic functionality can be employed to generate the organopalladium addend; however, the bimolecular reaction is strictly limited to unhindered alkenes. Thus, although a few examples of high yielding insertions of trisubstituted alkenes have been recorded, the vast majority of successful bimolecular Heck insertions involve mono- or disubstituted alkenes (ref. 1). Not surprisingly, intramolecularity can overcome the reluctance of substituted alkenes to participate in Heck reactions (ref. 2, 3) and in 1987 we reported that even tetrasubstituted alkenes can undergo intramolecular Heck arylations (ref. 3).



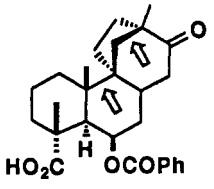
(±)-6a-epipretazettine



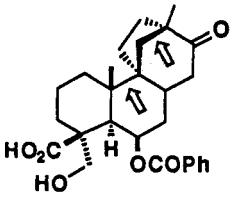
(±)-tazettine



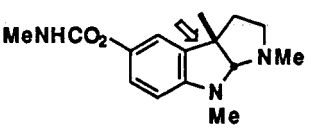
(-)- and (+)-morphine



(±)-scopadulcic acid B



(±)-scopadulcic acid A



(-)-and (+)-physostigmine

Fig. 1. Recently synthesized natural products containing critical quaternary carbon centers. Bonds to the quaternary centers prepared by intramolecular Heck reactions are shown with an arrow.

Being well aware of the difficulty that often attends the construction of congested quaternary carbon centers, it was clear to us that the ability to forge such centers by intramolecular Heck insertions of di-,

tri- and tetrasubstituted alkenes held enormous potential in the arena of complex molecule synthesis. As a result, our investigations in the intramolecular Heck area have focused nearly exclusively on quaternary center construction. In this brief review, I will highlight key aspects of this chemistry within the context of total syntheses of four structurally diverse families of natural products. Representative target structures that have now been synthesized in our laboratories using intramolecular Heck insertions to construct critical quaternary carbon centers are shown in Fig. 1 (ref. 4-8).

Total Synthesis of *Amaryllidaceae* Alkaloids. Eclipsed Topography of the Intramolecular Insertion Step. At the outset, we felt that detailed knowledge of the preferred orientation of the alkene π bond and palladium-carbon σ bond during the intramolecular insertion step would be essential to fully exploit intramolecular Heck insertions in stereorational organic synthesis. As a result, our first total synthesis targets were chosen to allow exploration of this issue at the experimental level (ref. 4). The [2]benzopyrano[3,4-c]hydroindole subgroup of *Amaryllidaceae* alkaloids, as exemplified by pretazettine (**3**) and 6a-epipretazettine (**4**), was targeted to provide an arena for exploring this stereochemical question (Fig. 2). The plan was to form the critical quaternary aryl carbon bond of these alkaloids by palladium catalyzed cyclization of **1** where, depending on the sense of stereoinduction, product **2** would be an obvious precursor of alkaloids **3** or **4**.

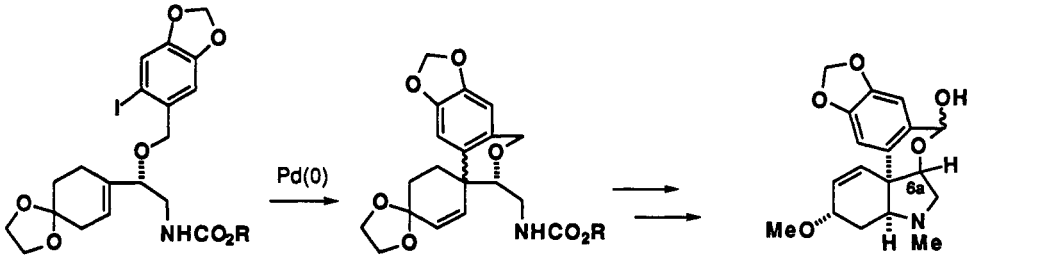


Fig. 2. Plan for total synthesis of *Amaryllidaceae* alkaloids containing the [2]benzopyrano[3,4-c]hydroindole partial structure.

Two possible conformations for the key suprafacial intramolecular insertion step are depicted in Fig. 3. If the aminomethyl side chain were disposed equatorially, insertion with an eclipsed orientation of the Pd-C σ and alkene π bonds would be possible if the tether adopted a boat-like conformation as shown in **5**. Insertion in this sense would lead to **7**, a product with the 6a-epipretazettine relative orientation at

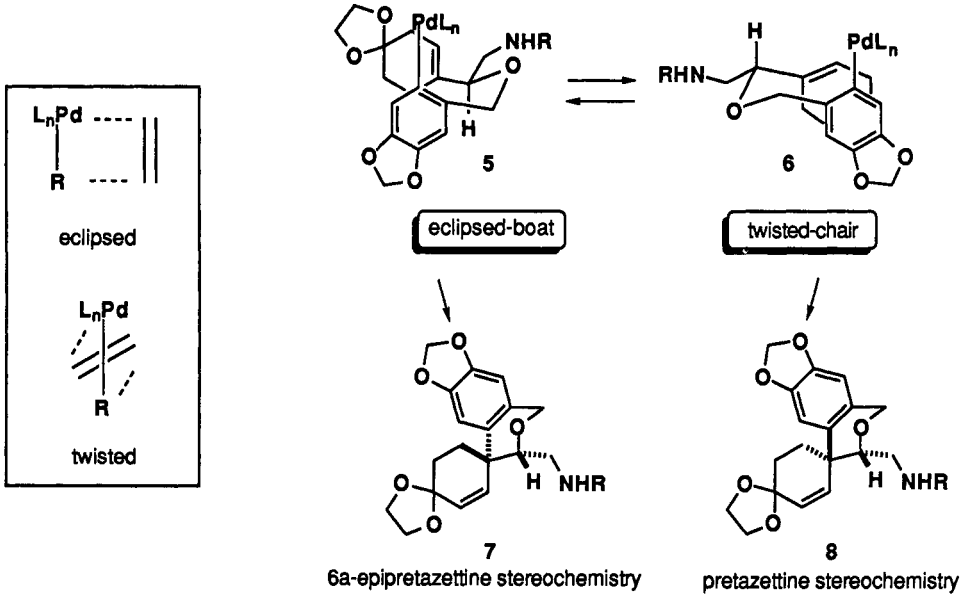


Fig. 3. Stereochemical outcome of eclipsed and twisted orientations of the Ar-Pd σ and alkene π bonds.

the newly formed quaternary carbon stereocenter. Coiling the tether in a chair conformation leads to a cyclization conformation having a twisted orientation of the Pd-C σ and alkene π bonds. Equatorial disposition of the side chain in this conformation **6** would evolve upon intramolecular insertion to **8**, having the stereochemistry of pretazettine. We note that in the ground state palladium(II)–alkene complexes typically exist with the alkene π bond perpendicular to the PdL_3 plane (a twisted orientation) (ref. 9).

The cyclization substrate **9** was prepared using straightforward chemistry in 8 steps and nearly 25% overall yield from *p*-methoxybenzyl alcohol (ref. 4). The pivotal cyclization of **9** could be carried out with a variety of palladium(0) catalysts and provided, within the detection limits of 500 MHz ^{1}H NMR spectroscopy, a single pentacyclic product **10** (Fig. 4). Reaction was fastest in the presence of silver salts (ref. 3, 10) and cyclization using the conditions described in Fig. 4 provided **10** in 90% yield (73% yield after recrystallization). Acidic treatment of this product resulted in cleavage of the ketal and concomitant cyclization to afford the crystalline [2]benzopyrano[3,4-c]hydroindole **11** in near quantitative yield. This pentacyclic intermediate proved amenable to single crystal X-ray diffraction

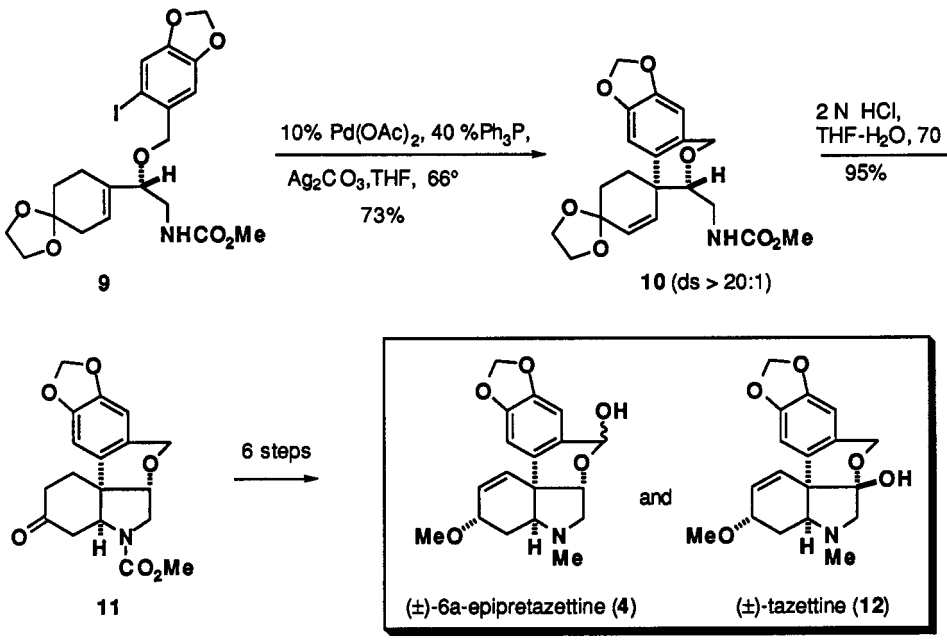


Fig. 4. Total Synthesis of (±)-6a-epipretazettine and (±)-tazettine. Experimental evidence for the eclipsed orientation of the C-Pd σ and alkene π bonds.

analysis which confirmed that cyclization had occurred preferentially to enter the 6a-epipretazettine stereoseries, thus *establishing a preference for an eclipsed orientation of the Pd-C σ and alkene π bonds in the key intramolecular insertion step.* In six additional steps, pentacycle **11** was converted to the *Amaryllidaceae* alkaloids (±)-tazettine (**12**) and (±)-6a-epipretazettine (**4**). Starting from commercially available *p*-methoxybenzyl alcohol 14 steps were required and the overall yields of **12** and **4** were ~4%.

Asymmetric Synthesis of Either Enantiomer of Opium Alkaloids and Morphinans. Total Syntheses of (-)- and (+)-Morphine. Natural opium alkaloids such as (-)-morphine (**20**), (-)-codeine and simpler morphinan and benzomorphan structural analogs are indispensable analgesics in the practice of medicine (ref. 11). We have recently described a total synthesis of natural and unnatural opium alkaloids and simpler morphinans that features an intramolecular Heck insertion as one of two key steps (ref. 5). The asymmetric total synthesis of (-)-morphine that is summarized in Fig. 5 introduces this versatile approach. The starting material, *(S)*-cyclohexenol **13**, was readily prepared by enantioselective reduction of 2-allylcyclohex-2-en-1-one with catecholborane in the presence of an *(R)*-oxazaborolidine catalyst (ref. 12). In a carefully optimized sequence, **13** was converted in 5 high yielding steps to the enantioenriched *(R)*-allylsilane amine **14** (91% ee). Condensation-cyclization of **14** with aryl acetaldehyde **15** proceeded with complete retention of absolute chirality and with high diastereoselection (ds >20:1) to provide octahydroisoquinoline **17** in 82 % yield. The stereochemical outcome of the iminium ion-allylsilane cyclization is rationalized by cyclization conformer **16**, in which the bulky dibenzosuberyl group is a critical stereocontrol element (ref. 13).

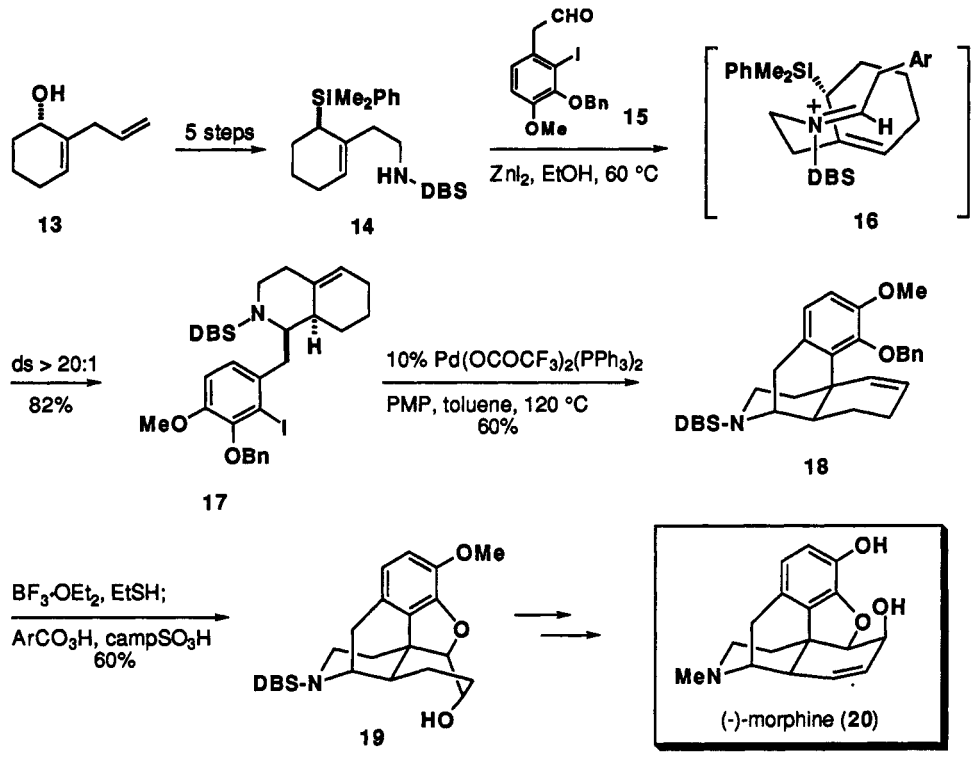


Fig. 5. Enantioselective synthesis of (-)-morphine (DBS = dibenzosuberyl).

Intramolecular Heck cyclization of **17** was best accomplished using 10 mol % of a reactive catalyst formed from $Pd(OCOCF_3)_2(Ph_3P)_2$ in refluxing toluene in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP) and gave the unsaturated morphinan **18** in 60% yield. After cleavage of the benzyl ether protecting group, the final ring of the opioid skeleton was formed by reaction of the camphorsulfonate salt of **18** with 3,5-dinitroperoxybenzoic acid to provide **19** in 60% yield. This pentacyclic intermediate was then transformed, by way of dihydrocodeinone, into enantioenriched (-)-morphine: $[\alpha]_D$ -119 ($CHCl_3$), 91%ee. In an identical fashion, *ent*-**13** was converted to enantioenriched (+)-morphine: $[\alpha]_D$ +118 ($CHCl_3$). These enantioselective syntheses are the first total syntheses of these opiates that do not involve resolution of an intermediate. One additional notable attribute of this organometallic route to morphinans and opium alkaloids should be noted. The pivotal intramolecular insertion step to form the tetracyclic morphinan skeleton can be accomplished with a

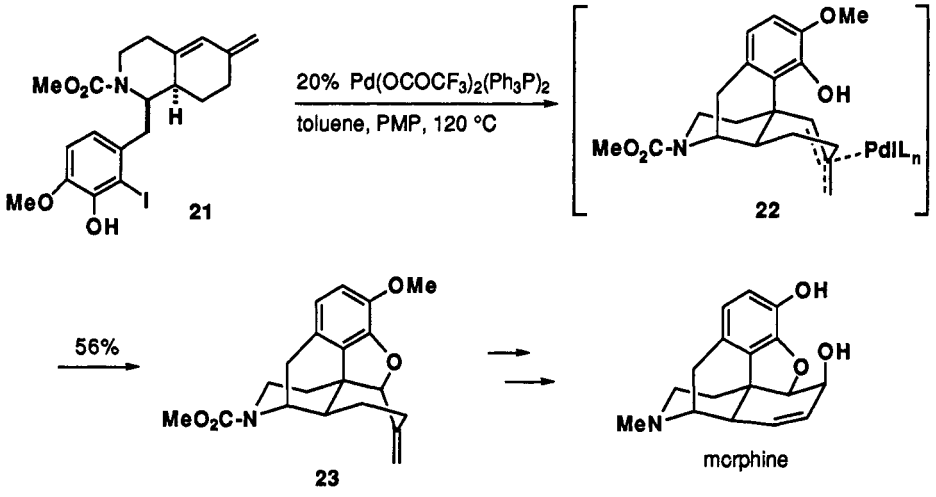


Fig. 6. Direct formation of opiates by palladium-catalyzed bis-cyclization.

wide variety of aryl and heteroaryl iodide precursors, importantly including ones that contain electron-deficient π-systems that would not be amenable to classical Grewe cyclization (ref. 14).

We have recently begun to investigate the appealing possibility of directly forming pentacyclic opiates from octahydroisoquinoline precursors by palladium-catalyzed bis-cyclization. Our initial success in this area is summarized in Fig. 6. Treatment of diene **21** under conditions similar to those we employed to form morphinans by Heck cyclizations (ref. 5), provided pentacycle **23** having the complete skeleton of the opium alkaloids (ref. 14). This conversion undoubtedly proceeds by initial Heck insertion to form the tetracyclic π-allyl palladium intermediate **22**, which then undergoes cis attack of the tethered alcohol on the π–allyl group, or, alternatively, stereomutation of the π–allyl moiety prior to trans addition of the alcohol (ref. 15).

Catalytic Asymmetric Synthesis of Either Enantiomer of Physostigmine and Congeners. High Enantioselection in Forming Quaternary Carbon Centers by Intramolecular Heck Reactions. Recent studies from our laboratories and those of Shibasaki and Hayashi have shown the substantial potential of asymmetric Heck reactions for preparing enantioenriched materials (ref. 16, 17). We were the first to demonstrate the direct asymmetric construction of quaternary carbon centers by intramolecular Heck reactions (ref. 16) and also to show, contrary to the existing conventional wisdom in this new area (ref. 17), that high enantioselection in the insertion of aryl substrates could be obtained in the presence of potentially coordinating halide counter ions (ref. 16b). For our first natural products application, we chose (-)-physostigmine (**28**), a naturally occurring alkaloid found in the seeds of African Calabar beans. Physostigmine is a powerful inhibitor of acetylcholinesterase and is employed clinically to treat glaucoma and myasthenia gravis (ref. 18). Of more current importance, (-)-physostigmine and congeners having enhanced pharmacokinetics are under active clinical investigation as potential therapeutic agents for treating Alzheimer's disease.

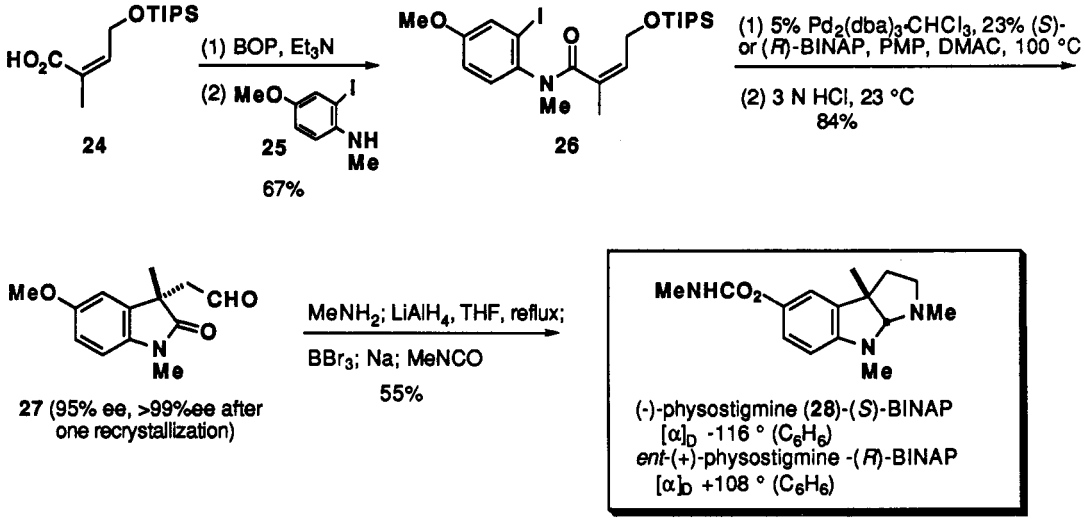


Fig. 7. Practical total synthesis of either enantiomer of physostigmine by asymmetric catalysis.

A practical method for preparing either enantiomer of physostigmine, and undoubtedly numerous analogs, is summarized in Fig. 7 (ref. 6). The pivotal conversion is the palladium-catalyzed cyclization of a (*Z*)-4-siloxy-2-methyl-2-butenanilide to form an enantioenriched 3,3-disubstituted-2-oxindole, a step that establishes the critical quaternary carbon center of the hexahydropyrrolo[2,3-b]indole ring system of physostigmine with excellent enantioselectivity (95% ee) (ref. 19). The sequence starts with the butenoic acid **24** (available in 3 steps and 70% yield from commercial 2-butyn-1-ol) which is first condensed with aniline **25** to provide **26**. Asymmetric Heck cyclization of **26** with 10 % Pd-(*S*)-BINAP (ref. 20) affords predominantly (98:2) the (*E*)-enoxysilane stereoisomer of the oxindole product. Hydrolysis of this material then provided the (*S*)-oxindole aldehyde **27** in 84% yield and 95% ee. A single recrystallization provided enantiopure **27** in 67% overall yield from anilide **26**. Sequential reaction of **27** with methylamine and $LiAlH_4$ afforded enantiomerically pure (-)-esermethole, which was transformed (as shown in Fig. 7) in two previously developed steps (ref. 21) to enantiopure natural (-)-physostigmine (**28**). Identical cyclization of **26** with Pd-(*R*)-BINAP lead to enantiopure (+)-physostigmine with similar efficiency. Two features of the central asymmetric cyclization step merit mention: (1) Asymmetric induction was optimal when the Pd-BINAP catalyst was formed in situ from 5% $Pd_2(dba)_3$·$CHCl_3$ and 23% BINAP, excess BINAP being employed to assure complete

complexation of Pd. (2) High enantioselection was critically dependent on the Z stereochemistry of the alkene group in **26**; the E isomer of related butenanilides cyclized under identical conditions with low asymmetric induction only (<50% ee) (ref. 6).

The First Total Syntheses of Scopadulcic Acids A and B. Application of Bis-Heck Cyclizations for Assembling Tetracyclic Diterpenes. In 1987 Hayashi and co-workers reported the isolation of two structurally novel acids, the scopadulcic acids A (**29**) and B (**30**), from the medicinal plant *Scoparia dulcis* L. (Scrophulariaceae) (Fig. 8) (ref. 22). Subsequent investigation has revealed a remarkable pharmacological profile for these tetracyclic diterpene acids: in vitro and in vivo antiviral and antitumor activities and powerful inhibitory activity against H^+, K^+-adenosine triphosphatase, an enzyme that is an important contemporary target for treatment of peptic ulcer disease (ref. 23). Our plan for the total synthesis of the scopadulcic acids is depicted in Fig. 8 and envisages construction of the BCD rings of these diterpenes, and the critical quaternary centers of the bicyclo[3.2.1]octane substructure, in a single step.

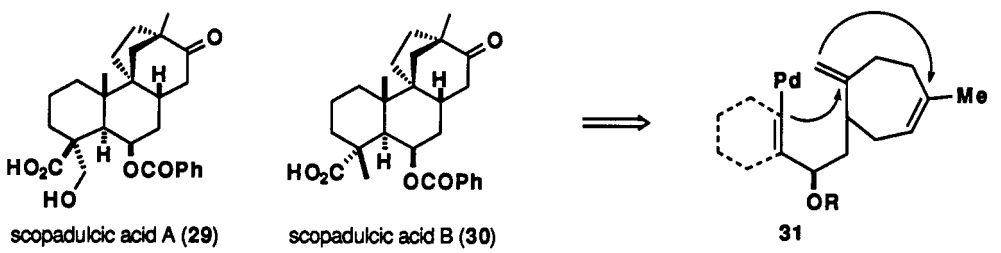


Fig. 8. Scopadulcic acids A and B and a plan for constructing them by bis-Heck cyclizations.

A bis-Heck cyclization of the methylenecycloheptenyl *o*-iodoaryl ketone **33** was the central step in our initial studies in this area, which culminated in the first total synthesis of (±)-scopadulcic acid B (Fig. 9) (ref. 7). The synthesis began with *o*-iodobenzaldehyde (**32**), which in 12 optimized steps was converted to **33** in ~20% overall yield on preparative scales. The critical bis-cyclization of dienyl aryl iodide **33** could be achieved with a variety of palladium(0) catalysts, although we found that preparative scale cyclizations were best carried out in refluxing acetonitrile in the presence of 5-10% of a coordinatively-unsaturated catalyst prepared from $Pd(OAc)_2$ and Ph_3P. Cyclizations conducted on scales as large as 14 g provided enones **34** in a combined yield of 80-85%. Contamination by the rearranged α,β-unsaturated ketone was minimized in cyclizations conducted in the presence of silver salts (ref. 3); however, no conditions completely suppressed double bond isomerization. Stereoselection in the initial insertion of the exomethylene group was not high, since the $\Delta^{13,14}$ enone was formed as 1.2-1.5:1 mixture of C(8) stereoisomers. Nonetheless, the sequence summarized in the

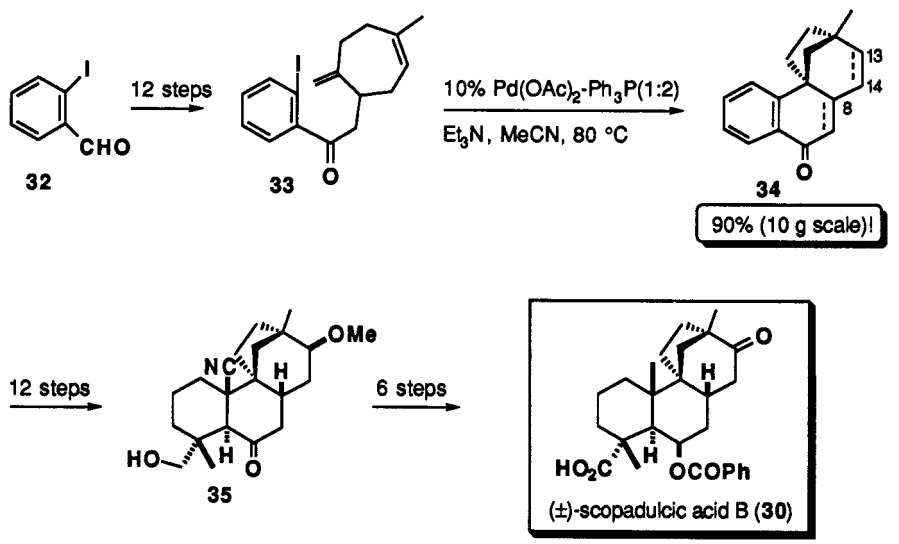


Fig. 9. First generation strategy: total synthesis of (±)-scopadulcic acid B.

top line of Fig. 9 provided a distinctively direct entry to the basic scopadulan ring system and provided a platform for the eventual completion of the first total synthesis of a scopadulan diterpene (ref. 7, 24).

As exemplified in the large number of steps required to convert enones **34** to the advanced scopadulcic acid B precursor **35** (Fig. 9), an aromatic ring is not an ideal template for developing the two quaternary centers of the scopadulan A ring. As a result, our second generation approach adopted a seco-A ring strategy in which bis-cyclization of a monocyclic trienyl iodide would be the central step (Fig. 10, **38** → **40**). This more direct total synthesis route to the scopadulan diterpenes successfully addresses several of the short-comings of our first generation approach. Notable is the complete stereocontrol now realized in the critical bis-Heck cyclization and the more direct elaboration from an acyclic precursor of the two quaternary centers of the scopadulan A ring.

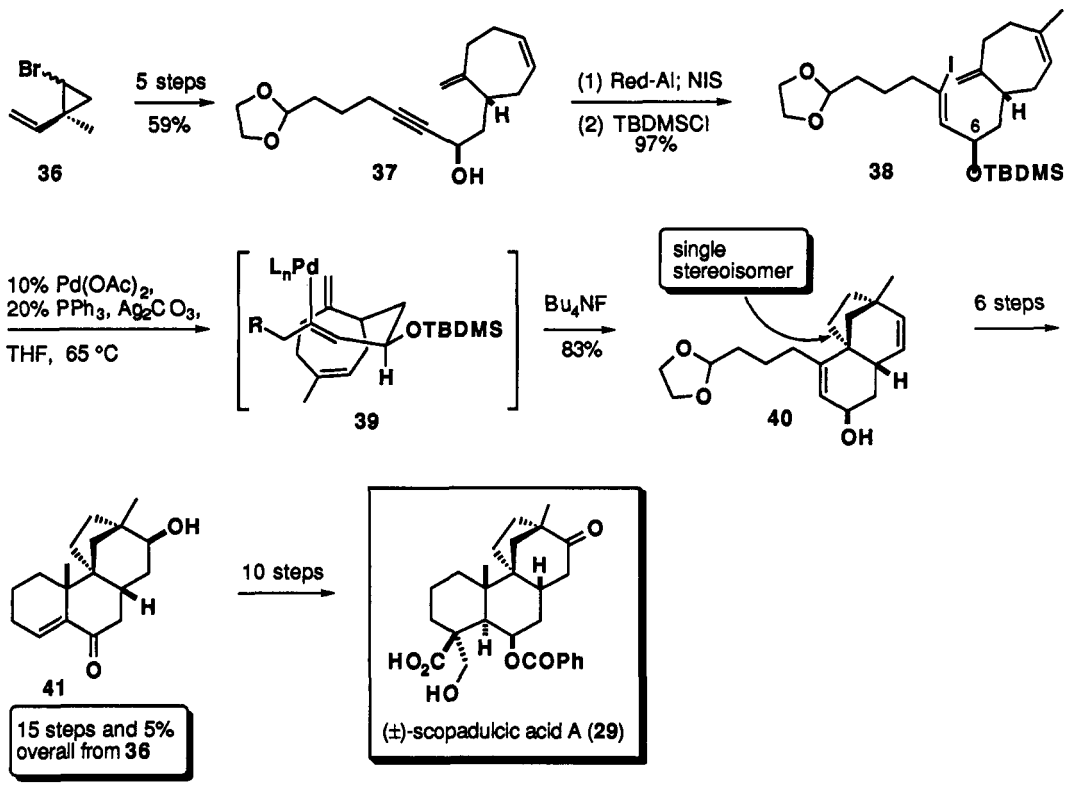


Fig. 10. Second generation seco A-ring strategy: total synthesis of (±)-scopadulcic acid A.

Our second generation synthesis begins with the cyclopropyl bromides **36**, which are available in one step from the dibromocarbene adduct of isoprene (ref. 8). Using divinylcyclopropane rearrangement chemistry related to that employed in our earlier synthesis of scopadulcic acid B (ref. 25), **36** was converted to **37**, which was then reduced and iodinated to provide the (Z)-trienyl iodide **38**. The salient bis-Heck cyclization of **38** proceeded cleanly in refluxing THF in the presence of 10% $Pd(OAc)_2$, 20% Ph_3P and 2 equiv of Ag_2CO_3 to give a *single* tricyclic product **40** in 82% yield, after desilylation. Stereoselection in this pivotal step is consistent with cyclization by way of conformer **39** where an eclipsed orientation of the C-Pd σ-bond and the exomethylene group places the siloxy substituent in an unhindered equatorial environment. The efficient sequence summarized in Fig. 10 provided **40** on multigram scales in 31% overall yield from the mixture of cyclopropyl bromides **36** (16% overall yield from isoprene). In six relatively straightforward steps, **40** was converted to the highly crystalline tetracyclic enone **41**, a versatile intermediate that undoubtedly will be useful for preparing a variety of scopadulan diterpenes and analogs. Enone **41** is available on preparative scales in 15 total steps and 5% overall yield from **36**. At this point, we have demonstrated this utility by the conversion of **41**, in 10 additional steps, to (±)-scopadulcic acid A (**29**) (ref. 8).

CONCLUSION

The total synthesis investigations summarized in this brief account confirm the utility of intramolecular Heck reactions for establishing demanding quaternary carbon centers in the synthesis of complex organic molecules. This powerful approach for constructing congested carbon skeleta is certain to be more widely used in the future.

ACKNOWLEDGMENTS

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