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Palladium-catalyzed polyene cyclizations

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Abstract. Palladium-catalyzed cyclizations of polyene aryl halides or enol triflates provide ready access to a wide variety of polycyclic carbon skeletons. General features of this chemistry as well as stereochemical aspects are discussed. The power of this organometallic chemistry is illustrated by the facile construction of the tetracyclic ring system of the scopadulcic acids.

The construction of polycyclic molecules from acyclic precursors is a general theme of biosynthesis. During the past 40 years, the laboratory synthesis of polycarbocyclic skeleta by biomimetic cyclizations of polyene cations, and more recently cyclizations of polyene radicals, has been developed to a high degree of sophistication and practical utility (refs. 1, 2). We recently initiated a program to develop a complementary polyene cyclization chemistry of organotransition metal intermediates (Fig. 1) (ref. 3). Although the polymerization of alkenes was one of the first important processes made possible by transition metal catalysis, in 1988, when our studies were initiated, the related assembly of polycyclic molecules from acyclic polyenes was largely undeveloped (ref. 4). Particularly appealing was the expectation that metal-mediated polyene cyclizations could provide polycyclic skeleta not readily available by cyclizations of carbenium ions or radicals. Polycyclizations of these latter two species are most effective when the electron-deficient intermediate can propagate at the more substituted termini of participating alkene units (ref. 5). In direct contrast, a polycyclization resulting from sequential intramolecular insertions of transition metal alkyls is expected to be most efficient when the transition metal propagates at the least substituted termini of the participating alkene units, e.g. **1** → **2** → **3**. This regiochemical preference should result from the thermodynamics of metal-carbon bonds, specifically the great decrease in the strength of the M-CR_3 σ bond as R is successively changed from hydrogen to carbon (ref. 6).

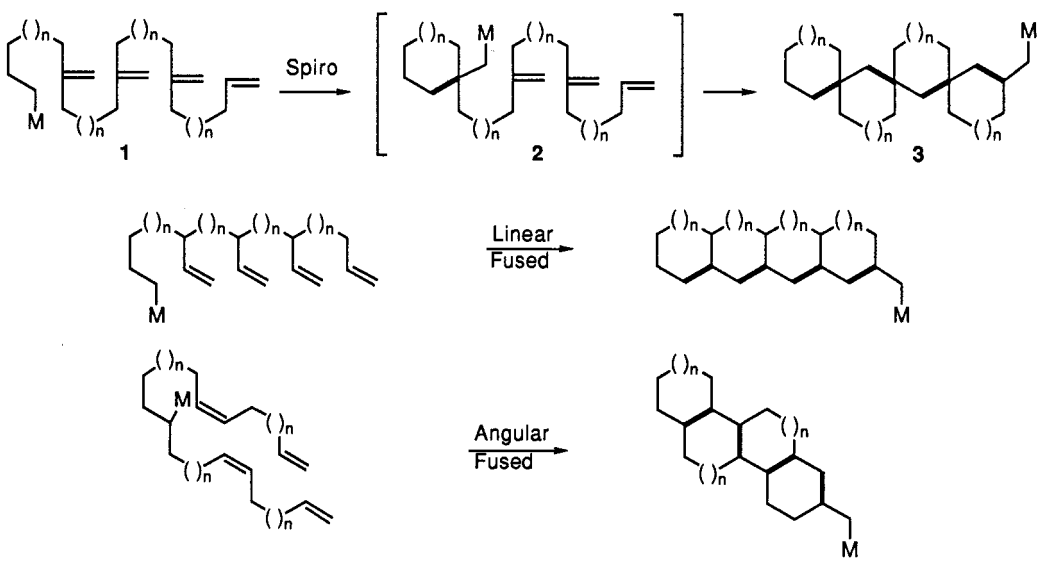


Fig. 1. Three potential topographies of metal-catalyzed polyene cyclizations. The new carbon-carbon bonds formed are in boldface print.

This account will focus on Heck-type polyene cyclizations of organopalladium intermediates. We will initially summarize several important general features of these reactions and then consider one specific application in the arena of complex molecule total synthesis. In this short account, important recent work in this area from other researchers, the groups of Grigg, Negishi, Oppolzer, Trost and others, must be omitted (ref. 8).

EXPLORATORY STUDIES

Polycyclizations of several representative dienyl and trienyl aryl iodides in the spirocyclic mode are shown in Fig. 2. Notable are the high overall yields and the mildness of the cyclization conditions. Although a variety of precursors of the palladium(0) catalyst can be employed, the use of mixtures of air stable palladium acetate and triphenylphosphine is particularly convenient. Heck-type cyclizations to form five-membered rings are typically faster than cyclizations to form cyclohexanes. Polycyclopentanoids such as **5** can often be prepared at room temperature using only a few percent of a relatively stable, tetra-ligated, palladium catalyst: **4** → **5** (ref. 3). If the first formed ring is six-membered, higher reaction temperatures and/or the use of a more reactive (and consequently less stable) catalyst with a phosphine to palladium ratio of < 4:1 is often required (e.g. the preparation of **8** and **10**). Although not required (see **7** → **8**), addition of a silver salt is often advantageous in minimizing migration of the initially formed exocyclic methylene group (refs. 3, 9). In the top three examples in Fig. 2, the palladium(0) catalyst is regenerated by palladium hydride elimination. The conversion of the trienyl aryl iodide **7** to pentacycle **10** provides one illustration of the myriad of possibilities that exist for further functionalization of the final organopalladium intermediates produced from the multiple insertion process (ref. 10). In this case, elimination of a β hydrogen is not possible and reduction of the neopentylpalladium intermediate **9** to afford the gem dimethyl group of pentacyclic **10** results. The yield of **10** increases with the concentration of triethylamine, demonstrating that this amine is the reducing agent.

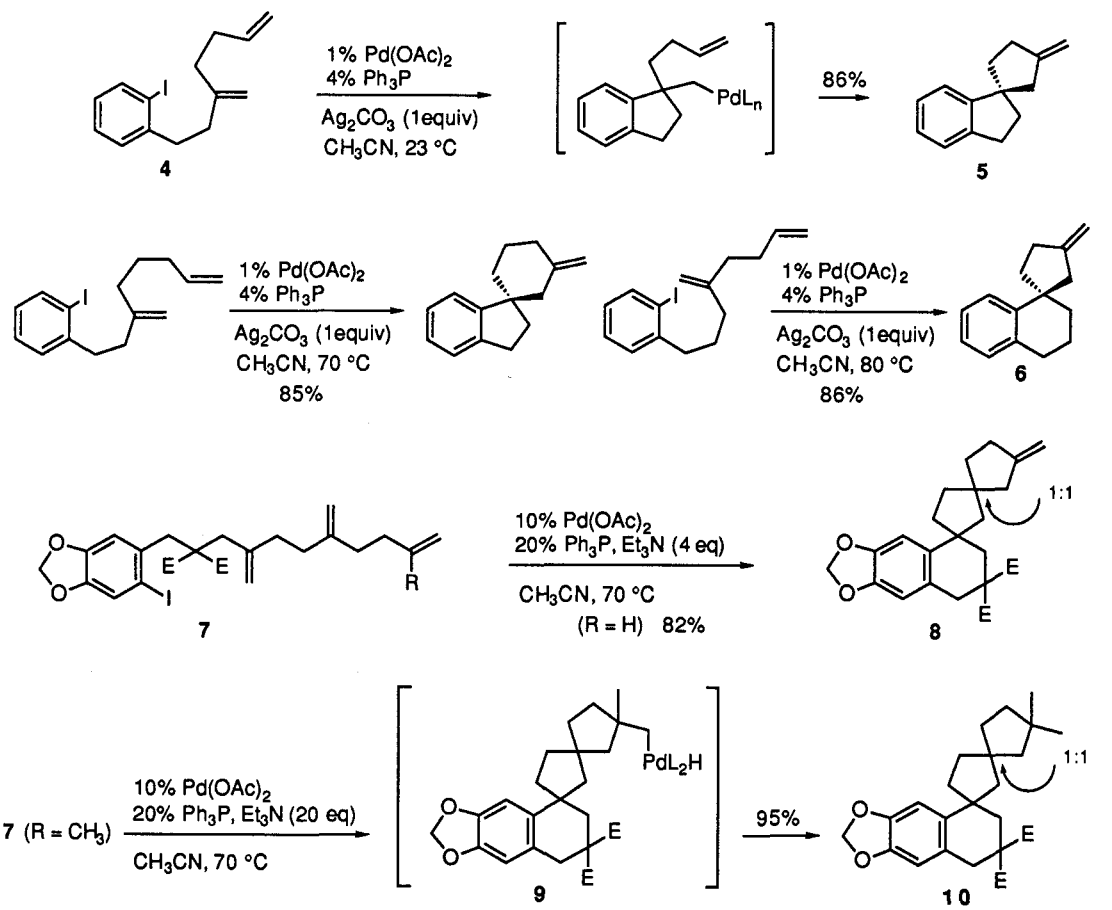


Fig. 2. Representative spirocyclic polycyclizations (E = CO_2Me).

The reactions shown in Fig. 3 examine the question of asymmetric induction at the newly formed quaternary center in cyclizations of dienyl aryl iodides containing stereocenters on the diene segment. When the stereogenic center is located on the tether connecting the aromatic ring with the proximal double bond, good stereoselection is obtained (ref. 3). Not surprisingly, little selectivity is realized when the stereogenic center is distal to the exo-methylene group of the cyclization precursor.

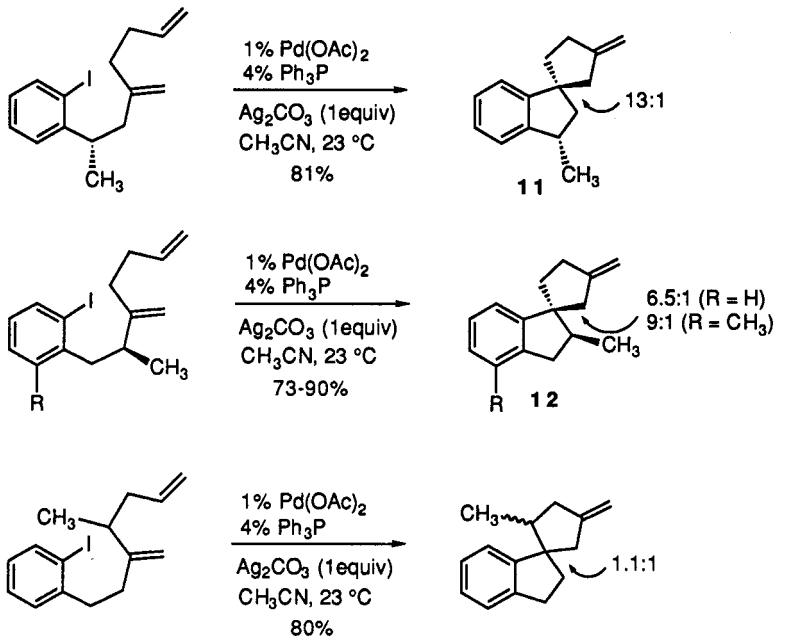


Fig. 3. Diasteroselection in forming the spirocyclic quaternary center. Stereochemistry of the major isomer is shown together with the stereoisomer ratio.

The preferential formation of spirocycles **11** and **12** (Fig. 3) is readily explained by an eclipsed alignment of the Pd-C σ and alkene π bonds in the first insertion step. A molecular mechanics model of an eclipsed transition state for the cyclization of the model alkene **13** is shown in Fig. 4. An equatorial orientation of the benzylic methyl substituent on the two atom tether minimizes non-bonded steric interactions between this group and the metal and phosphine ligands (phenyl in the real system). A recent investigation of the use of intramolecular Heck reactions to form quaternary carbon centers of *Amaryllidaceae* alkaloids provides further experimental verification of the preference for eclipsed (as opposed to twisted) orientations in intramolecular alkene insertions (ref. 11).

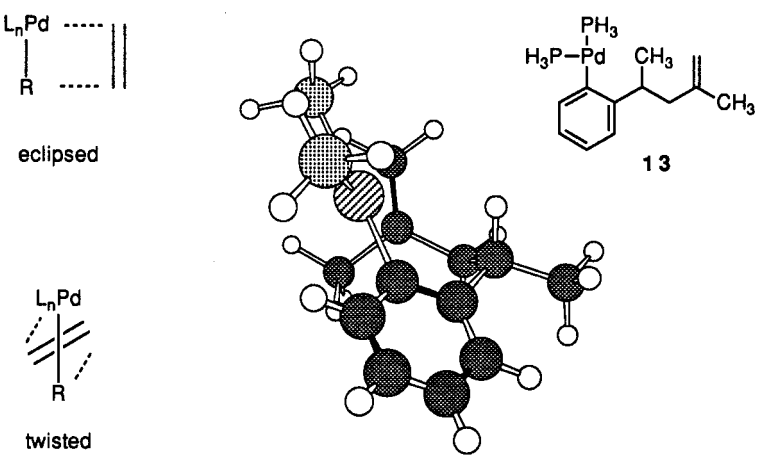


Fig. 4. Molecular mechanics model (MMX force field) of the eclipsed transition state for cyclization of **13**.

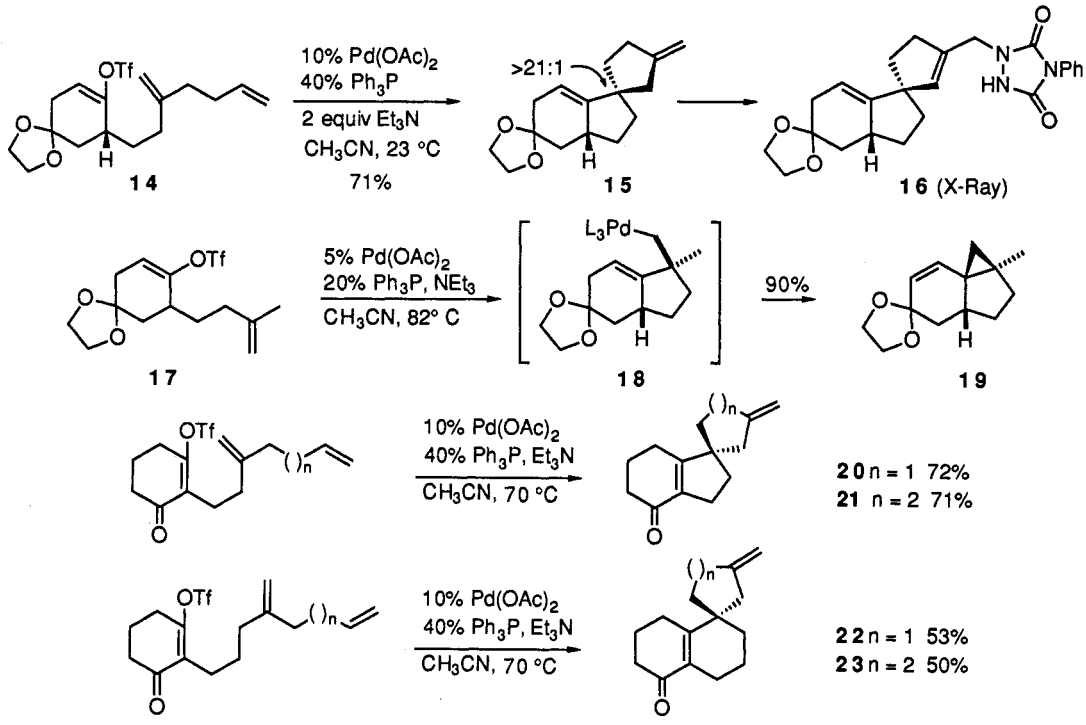


Fig. 5. Representative biscyclizations of unsaturated enol triflates.

Enol triflates are a particularly attractive class of cyclization substrates that are readily available from a variety of ketone precursors (ref. 12). Several examples of palladium-catalyzed biscyclizations of these intermediates are presented in Fig. 5. Extremely high diastereoselection is seen in the cyclization of the trienyl triflate **14**, which produces a single tricyclic product **15**. The stereochemistry of **15** was established by single crystal X-ray analysis of the ene product **16** produced from the reaction of **15** with 4-phenyl-1,2,4-triazoline-3,5-dione. The conversion of **17** to the cyclopropane-containing tricycle **19** is an unusual and efficient transformation that undoubtedly proceeds by way of **18** (ref. 13). Unfortunately, the high yield observed in this conversion is not general, since the homologue of **17** having a 4-methyl-4-pentenyl side chain affords the related tricycle in <40% yield. Initiation of the palladium-catalyzed cascade from an enol triflate derivative of a 1,3-diketone affords polycyclic products such as **20** - **23** that contain the versatile enone functionality (ref. 14). The ability to access these latter spirocycles in enantiomerically enriched form by palladium-catalyzed cyclizations that employ chiral, non-racemic, phosphine ligands has also been described (refs. 14, 15).

Although less well developed than spiro mode polycyclizations, palladium-catalyzed polyene cyclizations hold considerable promise for assembling fused polycyclic skeleta. Three representative examples from our investigations are shown in Fig. 6 (ref. 3).

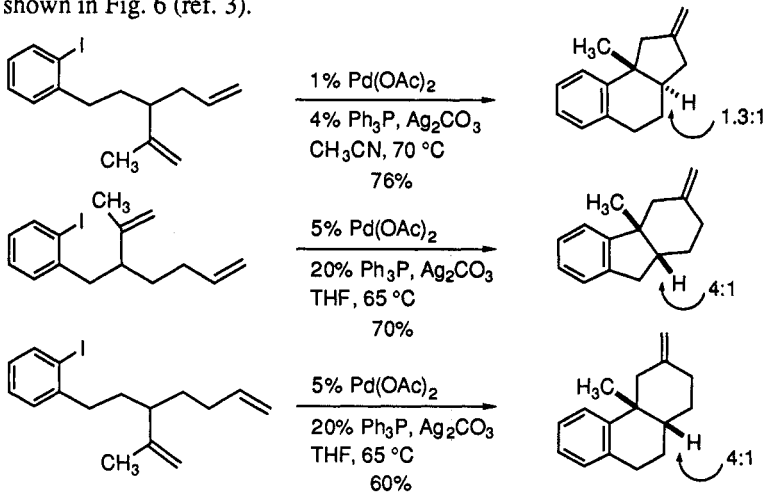
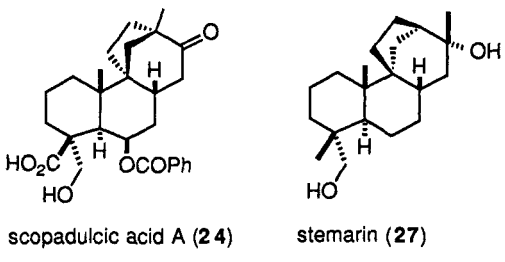


Fig. 6. Representative linear-fused polycyclizations. Stereochemistry of the major isomer is shown together with the stereoisomer ratio.

PROGRESS TOWARD THE TOTAL SYNTHESIS OF THE SCOPADULCIC ACIDS

The medicinal plant *Scoparia dulcis* L. has been used in Paraguay to improve digestion and protect against stomach disorders (ref. 16). In Taiwan, the same plant is used to cure hypertension, while in India it is used to treat toothaches, blennorhagia and stomach troubles (ref. 17). In recent investigations of Paraguayan *Scoparia dulcis* L., Hayashi and coworkers have isolated several new biologically active diterpenes exemplified by the scopadulcic acids A (**24**) and B (**25**) and scopadulciol (**26**) (Fig. 7) (ref. 19). The tetracyclic skeleton of these materials (termed the scopadulan ring system by Hayashi) is new, although it is related to that of several less-functionalized diterpenes such as stemarin (**27**) (ref. 19). Scopadulcic acid B and some derivatives are effective inhibitors of H^+, K^+ -adenosine triphosphatase and as such are potential candidates for treating peptic ulcers, gastritis or esophagitis (ref. 20). The antiviral activity of several scopadulan diterpenes against herpes simplex virus type 1 has also been described (ref. 21).



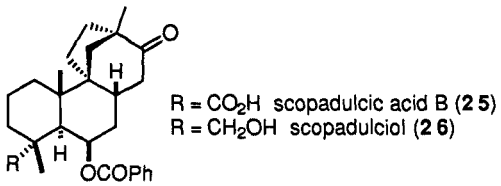


Fig. 7. Tetracyclic diterpenes with the scopadulan and stemaran skeletons.

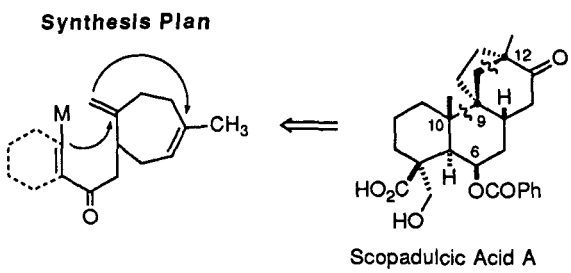


Fig. 8. Plan for constructing the B, C and D rings of the scopadulcic acids.

Figure 8 shows our plan for assembling the scopadulcic acids from a 5-methylenecycloheptene precursor. This unusual synthesis plan projects construction of the BCD ring system of the scopadulcic acids, and the important quaternary centers of the bicyclo[3.2.1]octane substructure, in a single step. To our knowledge, there is no existing synthetic chemistry that could arguably achieve the construction suggested in Fig. 8.

In an early model study, we examined the cyclization of dienyl aryl iodide **28**, an intermediate that lacks the methyl substituent at C(12) of the cycloheptene ring (ref. 3). This simpler system was chosen for initial investigation for two reasons: (a) diene **28** could be readily assembled from 2-carbomethoxy-4-cyclohepten-1-one (ref. 22) and (b) the second step in the projected biscyclization would be particularly favorable since it would involve insertion of a disubstituted (rather than a trisubstituted) double bond. In the event, cyclization of **28** under standard conditions occurred cleanly to form two major tetracyclic hydrocarbons, **29** and **30**, which were isolated in 52% and 40% yields, respectively. Extensive 2D NMR

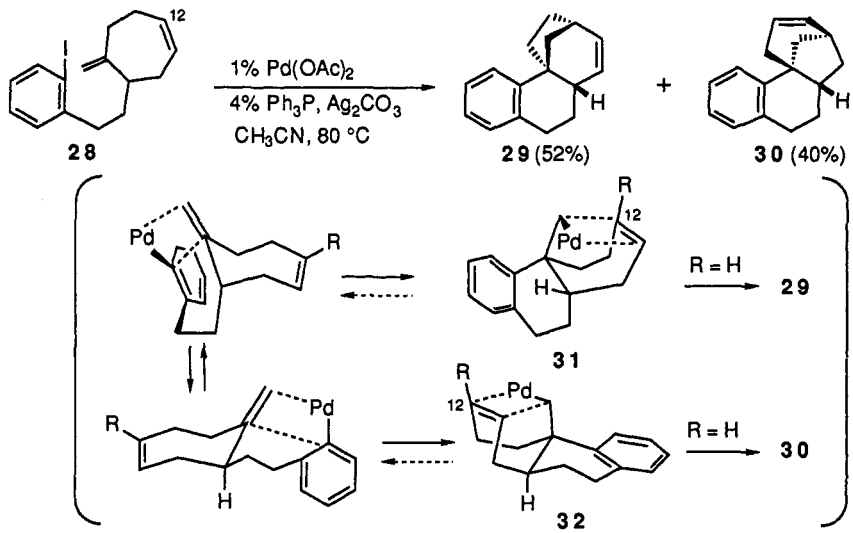


Fig. 9. First model study towards the scopadulcic Acids. Formation of the hydrocarbon ring system.

and ^1H NOE studies established that the major product **29** had the desired tetracyclic skeleton. In principle, four hydrocarbons could have been formed from cyclization of **28**. The fact that **29** and **30** strongly predominate demonstrates that the tricyclic intermediates **31** and **32**, which result from insertion into the two faces of the exo-methylene group, both undergo highly regioselective insertion of the disubstituted cycloheptene double bond.

Buoyed by the success of this model study, we turned to a substrate that incorporated the methyl substituent at C(12) and oxidation at C(6). The synthesis of such a cyclization precursor, dienone **35**, is outlined in Fig. 10. This sequence has been optimized and affords **35** on a multigram scale in 20 - 25% overall yield from 2-iodobenzaldehyde. A divinylcyclopropane rearrangement of the enoxysilane derivative of a cyclopropyl ketone, **33** → **34**, is the key strategic step in this sequence (ref. 23).

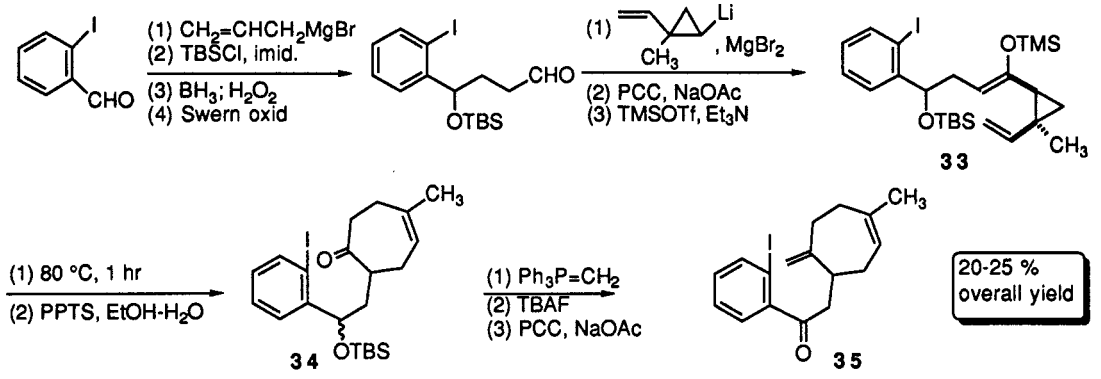


Fig. 10. Synthesis of cyclization precursor **35**.

Much to our delight, the pivotal cyclization of dienone aryl iodide **35** occurred cleanly to afford the desired tetracyclic skeleton of the scopadulcic acids (Fig. 11). Isolated in high yields from cyclizations of **35** conducted on scales as large as 10 grams are the two C(8) epimers of tetracycle **36**. Cyclizations carried out without silver carbonate but in the presence of triethylamine occurred in nearly quantitative yield to give mixtures of **36** and the conjugated B ring enone. The structure of **36** was confirmed by epoxidation with *m*-chloroperoxybenzoic acid, which took place cleanly from the face of the one carbon bridge, to give the two epoxides **37** and **38**. The epoxide **38**, derived from the minor isomer of **36**, provided suitable crystals for single crystal X-ray analysis. The high predilection of palladium-catalyzed polyene cyclizations to occur with propagation of the Pd-C bond at the less-substituted terminus of participating π-bonds is apparent in the cyclization of **35**. Clearly, a methyl substituent at C(12) is sufficient to prevent the intermediate trans-fused ABC tricycle (**32**, R = CH_3) from inserting in the direction shown in Fig. 9, which would have led to an intermediate with a tertiary carbon palladium σ bond and afforded the methyl analog of **30**.

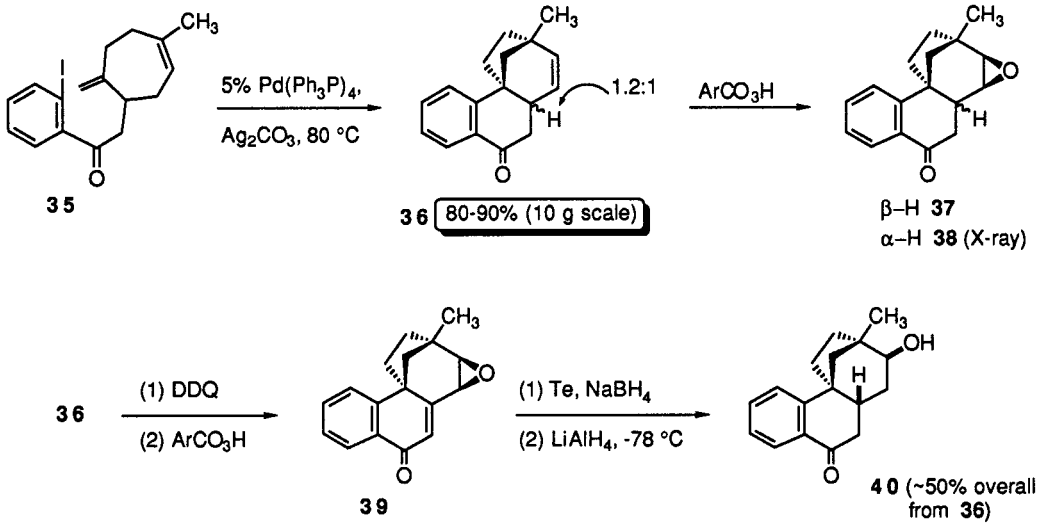


Fig. 11. Formation of the tetracyclic skeleton of the scopadulcic acids.

In one approach we are pursuing for completing this total synthesis endeavor, the two epimers of **36** are converged by dehydrogenation to the dienone. This intermediate can then be selectively epoxidized to afford **39**, a transformation that again occurs cleanly from the less-hindered face of the bicyclo[3.2.1]octane ring system. Reductive ring opening of **39**, followed by hydroxyl directed reduction of the resulting conjugated enone, provides **40** in good overall yield from the Heck bis-cyclization product **36**. Tetracycle **40** contains the full carbon skeleton of rings B, C and D of the scopadulcic acids as well as the required oxidation at carbons 6 and 13 of these target molecules.

CONCLUSION

In less than five years palladium-catalyzed polyene cyclizations have emerged as a powerful strategy for assembling polycyclic ring systems. Our successful introduction of this chemistry into the arena of complex molecule construction (ref. 11), perhaps best exemplified by the conversion of **35** → **36**, should stimulate further developments in this area. In light of the current extensive efforts world-wide directed at metal-based cyclization strategies, we can look to a future time when organometallic methods occupy a position of comparable importance in polycycle construction to that currently occupied by cyclization reactions of carbenium ions and free radicals.

Acknowledgements

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REFERENCES

1. (a) W. S. Johnson, Bioorg. Chem. 5, 51 (1976). (b) P. A. Bartlett, Asymmetric Synthesis, Stereodifferentiating Addition Reactions Part B, 3, Academic, New York (1984).
2. D. P. Curran, Synthesis, 489 (1988).
3. M. M. Abelman and L. E. Overman, J. Am. Chem. Soc. 110, 2328 (1988),
4. J. P. Collman, L. S. Hegedus, J. R. Norton and R. G. Finke, Principles and Applications of Organotransition Chemistry, University Science Books, Mill Valley, CA (1987).
5. W. S. Johnson, S. J. Telfer, S. Cheng and U. Shubert, J. Am. Chem. Soc. 109, 2517 (1987)
6. W. Jones, Acct. Chem. Res. (1989).
7. R. F. Heck, Organic Reaction (NY), 27, 345 (1982).
8. For leading references to the work of other laboratories, see: (a) B. M. Trost and Y. Shi, J. Am. Chem. Soc. 113, 701 (1991). (b) Y. Zhang, G. Wu, G. Agnel and E. Negishi, J. Am. Chem. Soc. 112, 8590 (1990). (c) R. Grigg, V. Loganathan, S. Sukirthalingam and V. Sridharan, Tetrahedron Lett. 31, 6573 (1990). (d) W. Oppolzer, Angew. Chem., Int. Ed. Engl. 28, 38 (1989).
9. M. M. Abelman, T. Oh and L. E. Overman, J. Org. Chem., 52, 4130 (1987).
10. These possibilities have been most extensively examined by Grigg (ref. 8c).
11. M. M. Abelman, L. E. Overman and V. D. Tran, J. Am. Chem. Soc., 112, 6959 (1990).
12. W. E. Scott and J. E. McMurry, Acc. Chem. Res. 21, 47 (1988).
13. Other examples of "back" insertions to form cyclopropanes have been reported by Negishi; see: Y. Zhang and E. Negishi, J. Am. Chem. Soc. 111, 3454 (1989).
14. N. E. Carperter, D. J. Kucera and L. E. Overman, J. Org. Chem., 54, 5846 (1989).
15. For leading references to other asymmetric Heck reactions, see: (a) Y. Sato, S. Watanabe and M. Shibasaki, Tetrahedron Lett. 33, 2589 (1992). (b) F. Ozawa, A. Kubo and T. Hayashi, J. Am. Chem. Soc. 113, 1417 (1991). (c) A. Ashimori and L. E. Overman, J. Org. Chem. 57, in press (1992).
16. D. M. Gonzales Torres, Catalogo de Plantas Medicinales (y Alimenticias y Utiles) Usada en Paraguay, Asunción, Paraguay, 394 (1986).
17. (a) S. Y. Chow, S. M. Chen, C. M. Yang and H. Hsu, J. Formosan Med. Assoc. 73, 729 (1974). (b) K. Satyanarayana, J. Indian Chem. Soc. 46, 765 (1969).
18. (a) T. Hayashi, M. Kishi, M. Kawasaki, M. Arisawa, M. Shimizu, S. Suzuki, M. Yoshizaki, N. Morita, Y. Tezuka, T. Kikuchi, L. H. Berganza, E. Ferro and I. Basualdo, Tetrahedron Lett. 28, 3693 (1987). (b) T. Hayashi, S. Asano, M. Mizutami, N. Takeguchi, T. Kojima, K. Okamura and N. Morita, J. Natural Prod. 54, 802 (1991). (c) M. Ahmed and J. Jakupovic, Phytochem. 29, 3035 (1990).
19. (a) P. S. Manchand and J. F. Bount, J. Chem. Soc., Chem. Commun. 894 (1975). (b) F. Bohlmann, C. Zdero, R. M. King and H. Robinson, Justus Liebigs Ann. Chem. 250, (1984).
20. T. Hayashi, K. Okamura, M. Kakemi, S. Asano, M. Mizutani, N. Takeguchi, M. Kawasaki, Y. Tezuka, T. Kikuchi and N. Morita, Chem. Pharm. Bull. 38, 2740 (1990).
21. T. Hayashi, K. Hayashi, K. Uchida, S, Niwayama and N. Morita, Chem. Pharm. Bull. 38, 239 (1990).
22. R. F. Borch and B. C. Ho, J. Org. Chem. 42, 1225 (1977).
23. P. A. Wender, M. A. Eissenstat and M. P. Filosa, J. Am. Chem. Soc. 101, 2196 (1979).