JOC*Note*

General Approach to Polycyclic Meroterpenoids Based on Stille Couplings and Titanocene Catalysis

José Justicia, J. Enrique Oltra, and Juan M. Cuerva*

Department of Organic Chemistry, Faculty of Sciences, University of Granada, E-18071 Granada, Spain

jmcuerva@platon.ugr.es

Received May 3, 2004

Abstract: We describe a novel convergent procedure that has proved useful in the synthesis of a wide range of meroterpenoid-related structures containing a mono-, sesqui-, or diterpenoid moiety linked to a nonfused aromatic subunit with various substitution patterns. The key steps were the Stille-type coupling of aryl stannanes and allylic carbonates, followed by the titanocene-catalyzed domino cyclization of aryl epoxypolyprenes. The coupling reaction was perfectly compatible with preformed epoxides, while the sequential cyclization, which presumably proceeded via alkyl radicals inert to benzene derivatives, selectively provided exocyclic alkenes.

The word "meroterpenoids" is generally used to denote a wide range of natural products of mixed (polyketide-terpenoid) biogenesis.[1] Among the meroterpenoids there occur both marine and fungal metabolites that share a common structural feature: their molecules are formed by a quinone, hydroquinone, or closely related subunit linked to a cyclic terpenoid moiety by at least one C−C bond. As relevant examples we might cite marine natural products such as cyclocymopol (**1**), zonarol (**2**), pelorol (**5**), stypoldione (**6**), and taondiol (**7**) or fungal metabolites such as K-76 (**3**) and kampanol A (**4**) (Figure 1).[2] Several of these products have attracted the attention of synthetic chemists[3] because of their interesting pharmacological properties such as antifungal,[2b] antiinflammatory,[2c] or *ras* farnesyl-protein transferase inhibitory activity[2d] or severe ichthyotoxic effects.[2g]

Two different strategies have generally been employed for the chemical synthesis of polycyclic meroterpenoids: (a) the biomimetic[4] sequential cyclization of prenylated hydroquinones, as used by Gonzalez et al.[3a,b] for the synthesis of taondiol (**7**), and (b) a two-synthon strategy (Scheme 1) introduced by Corey and Das[3c] for the synthesis of K-76 (**3**), which has subsequently been used by several other chemists despite the often troublesome procedure required for the preparation of the polycyclic terpenoid synthon.[3d−i]

Sequential reactions generally comply with the selectivity and atom- and step-economy requirements needed in contemporary chemistry[5] and are consequently regarded as powerful synthetic tools.[6] Nevertheless, the sequential cyclization described by Gonzalez et al.[3a,b] has received scarce attention, possibly due to the limitations imposed by the carbocationic nature of a process initiated by the acid-induced epoxide opening used by these authors. In fact, the tertiary carbocation formed at the end of epoxypolyprene cyclization is effectively trapped by one of the nucleophilic oxygen atoms of the hydroquinone moiety,[3a,b] thus facilitating the preparation of taondiol (**7**) but at the same time seriously hindering the potential synthesis of other meroterpenoids, including zonarol (**2**), K-76 (**3**), and stypoldione (**6**), with stronger biological activity. Moreover, tertiary carbocations are electrophilic enough to attack accessible positions of the

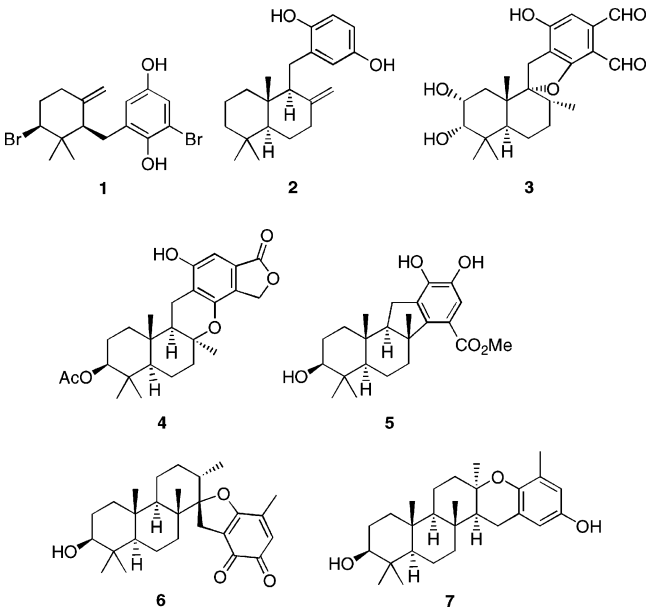


FIGURE 1. Various fungal and marine meroterpenoids.

* Corresponding author. Fax: +34 958 248437.

(1) Simpson, T. *J. Top. Curr. Chem.* **1998**, *195*, 1−48.

(2) Isolation: (a) Cyclocymopol: Högberg, H.-E.; Thomson, R. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1696. (b) Zonarol: Fenical, W.; Sims, J. J.; Squatrito, D.; Wing, R. M.; Radlick, P. *J. Org. Chem.* **1973**, *38*, 2383. (c) K-76: Kaise, H.; Shinohara, M.; Miyazaki, W.; Izawa, T.; Nakano, Y.; Sugawara, M.; suwagara, K. *Chem. Commun.* **1979**, 726. (d) Kampanol A: Singh, S. B.; Zink, D. L.; Willians, M.; Polishook, J. D.; Sanchez, M.; Silverman, K. C.; Lingham, R. B. *Biorg. Med. Chem. Lett.* **1998**, *8*, 2071. (e) Taondiol: Gonzalez, A. G.; Darias, J.; Martín, J. D. *Tetrahedron Lett.* **1971**, 2729. (f) Pelorol: Kwak, J. H.; Schmitz, J.; Kelly, M. *J. Nat. Prod.* **2000**, *63*, 1153. (g) Stypoldione: Gerwick, W. H.; Fenical, W.; Fritsch, N.; Clardy, J. *Tetrahedron Lett.* **1979**, *14*, 145.

(3) For some selected reports on synthesis of fungal and marine meroterpenoids, see: (a) Gonzalez, A. G.; Martín, J. D.; Rodríguez, M. L. *Tetrahedron Lett.* **1973**, *14*, 3657. (b) Gonzalez, A. G.; Martin, J. D.; Rodriguez, M. L. *An. Quim.* **1976**, *72*, 1004. (c) Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551. (d) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712. (e) Begley, M. J.; Fish, P. V.; Pattenden, G.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2263. (f) Tsujimori, H.; Bando, M.; Mori, K. *Eur. J. Org. Chem.* **2000**, 297. (g) Takao, K.; Sasaki, T.; Kozaki, T.; Yanagisawa, Y.; Tadano, K.; Kawashima, A.; Shinonaga, H. *Org. Lett.* **2001**, *3*, 4291. (h) Takikawa, H.; Hirooka, M.; Sasaki, M. *Tetrahedron Lett.* **2002**, *43*, 1713. (i) Iwasaki, K.; Nakatani, M.; Inoue, M.; Katoh, T. *Tetrahedron* **2003**, *59*, 8763.

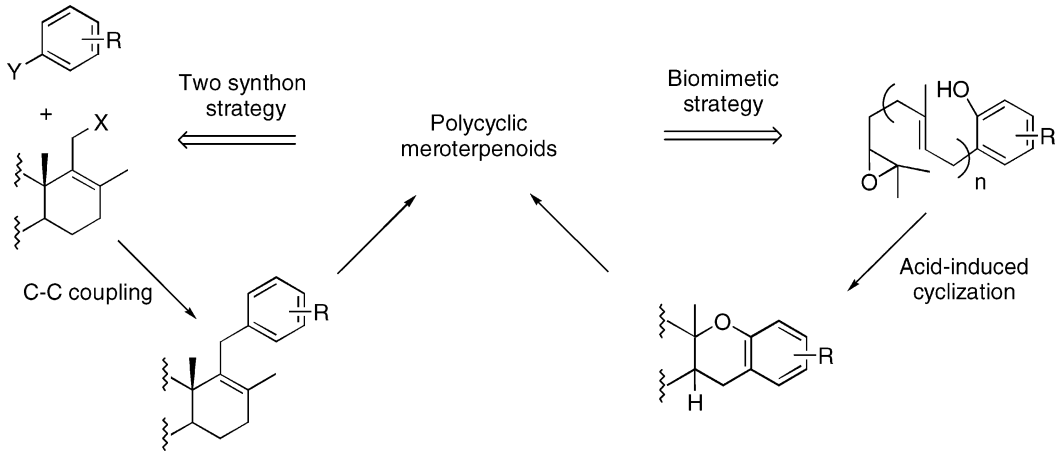
(4) Co-occurrence of polycyclic meroterpenoids with other metabolites showing an acyclic terpenoid moiety (see ref 2a for instance) suggests that, in the biosynthesis of meroterpenoids, the polyene cyclization takes place after the C−C linkage between the terpenoid and the polyketide subunits; see ref 3e.

(5) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Fürstner, A. *Synlett* **1999**, 1523. (d) Furstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *115*, 320.

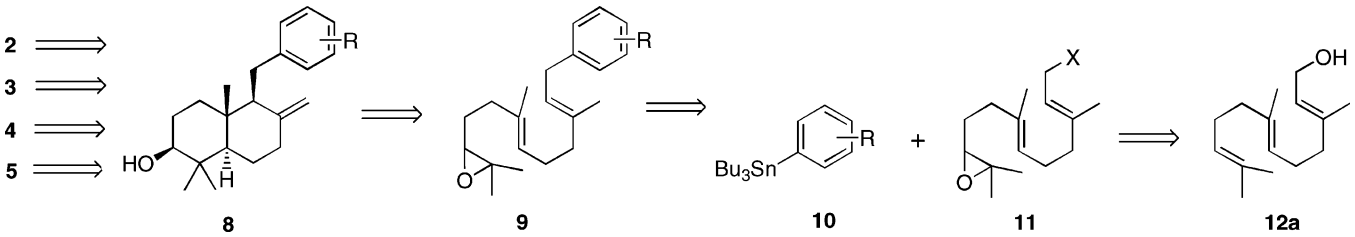
(6) For reviews on "sequential" (also dubbed "cascade" or "domino") reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Malacria, M. *Chem. Rev.* **1996**, *96*, 289.

10.1021/jo049253r CCC: $27.50
Published on Web 07/23/2004

SCHEME 1. Synthetic Strategies to Obtain Polycyclic Meroterpenoids



SCHEME 2. Retrosynthetic Analysis to Polycyclic Meroterpenoids.



neighboring aromatic rings in a well-known reaction[7] that could lead to undesired byproducts.

Alkyl radicals, on the other hand, are generally compatible with hydroxyl groups; furthermore, homolytic aromatic substitution is usually a slow reaction.[8] Therefore, radical cyclizations might well overcome the drawbacks of the cationic processes mentioned above. With this idea in mind, we planned a novel procedure for the synthesis of polycyclic meroterpenoids from commercial acyclic polyprenols such as farnesol (**12a**) based on Stille coupling with aryl stannanes (such as **10**) followed by the titanocene-catalyzed[9] radical cyclization of the corresponding aryl epoxypolyprenes (such as **9**) (Scheme 2). In this way, our previous experience with titanocene catalysis suggested that, using the combination Mn/Me_3-SiCl/collidine as titanocene-regenerating agent, the radical cyclization would give versatile intermediates with an exocyclic double bond (such as **8**),[10] closely related to zonarol (**2**) and also suitable to be easily transformed into sesquiterpenoids **3**−**5**. Moreover, this strategy could be extended to the synthesis of other types of meroterpenoids, including **1**, **6**, and **7** by simply replacing the starting material **12a** with the commercially available homologues geraniol (**12b**) or geranylgeraniol (**12c**).

To check our hypothesis, we decided to synthesize a set of epoxypolyprenes linked to aromatic rings containing different functionalization patterns, by means of a Stille-type coupling between allylic carbonates and aryltrialkylstannanes developed by Echavarren's group (see Scheme 3).[11] To this end we prepared different stannanes (**10a**−**f**) from commercial aryl bromides under the conditions described by Morita et al.,[12] obtaining yields ranging from 66 to 99%. We then prepared allylic carbonates **14a**−**c** by stirring sodium hydride and diethyl carbonate with epoxypolyprenols **13a**−**c**, easily obtained from the corresponding precursors **12a**−**c** as reported elsewhere.[10b] Finally, the Stille coupling between different aryl stannanes (**10**) and carbonates **14a**−**c** under Echavarren's conditions provided aryl epoxypolyprenes **15**−**23** at yields ranging from 66 to 92% (Scheme 3, Table 1),[13] confirming that this reaction is perfectly compatible with preformed oxiranes.

(7) (a) Ishiara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (b) Rosales, V.; Zambrano, J. L.; Demuth, M. *J. Org. Chem.* **2002**, *67*, 1167.

(8) For a recent overview on contemporary free-radical chemistry, see: *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.

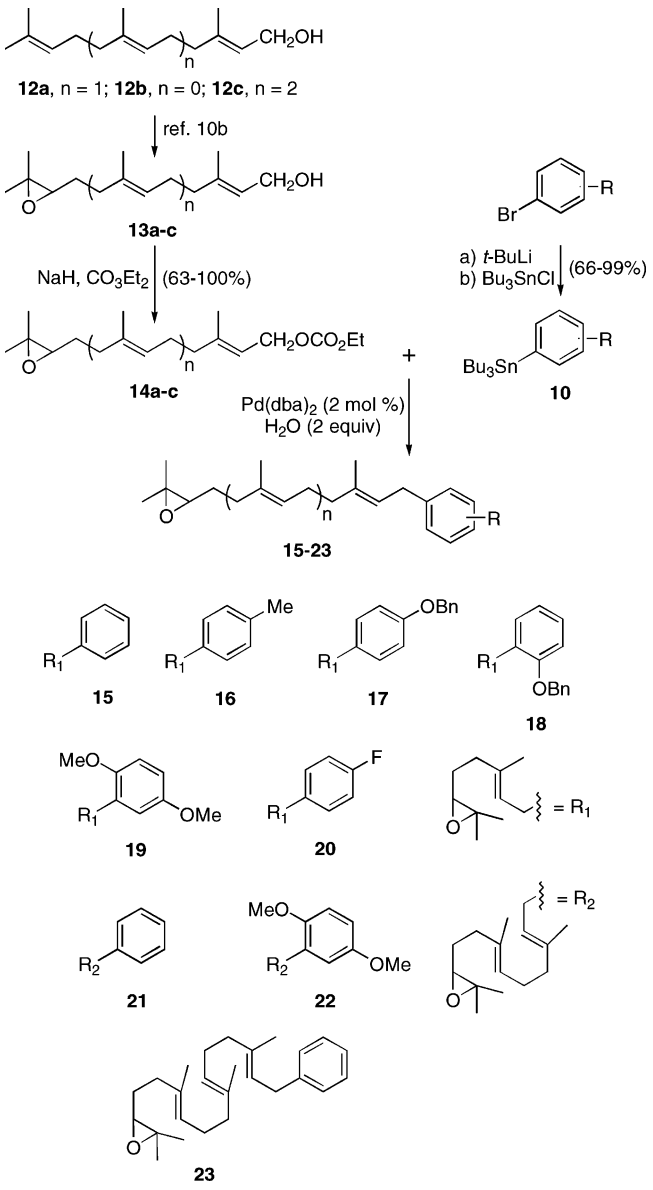
(9) For seminal works on titanocene-mediated epoxide openings, see: (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986. For seminal works on titanocene-catalyzed epoxide openings, see: (b) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101. (c) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849. For recent reviews, see: (d) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (e) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103. (f) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556.

(10) Some titanocene(III)-catalyzed processes can be controlled to end in the formation of an exocyclic double bond, by working under anhydrous conditions and using Me_3SiCl/2,4,6-collidine to regenerate Cp_2TiCl_2; see: (a) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2003**, *5*, 1935. (b) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778. This procedure has been previously used in the synthesis of other types of natural products: (c) Justicia, J.; Oltra, J. E.; Cuerva, J. M. *Tetrahedron Lett* **2004**, *45*, 4293−4296. Another titanocene-regenerating agent has been recently reported: (d) Fuse, S.; Hanochi, M.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2004**, *45*, 1961.

(11) For a seminal work on coupling of allylic acetates, see: (a) Del Valle, L.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019. For couplings of allylic carbonates, see: (b) Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1996**, *37*, 6587. (c) Castaño, A. M.; Mendez, M.; Ruano, M.; Echavarren, A. M. *J. Org. Chem.* **2001**, *66*, 589

(12) Morita, Y.; Kashiwagi, A.; Nakasuji, K. *J. Org. Chem.* **1997**, *62*, 7464.

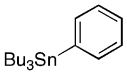
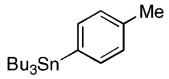
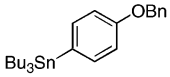
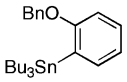
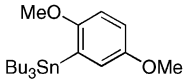
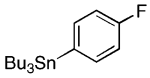
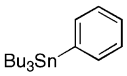
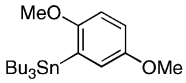
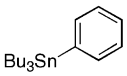
SCHEME 3. Synthesis of Aryl Epoxypolyprenes 15−23



Subsequently, epoxides **15**−**23** were stirred with a substoichiometric quantity of commercial Cp_2TiCl_2 (20 mol %), Mn dust, and Me_3SiCl/2,4,6-collidine in dry THF at room temperature, giving cyclization products **24**−**32**, respectively, in moderate yields ranging from 35 to 55% (Scheme 4). Nevertheless, even the lowest yield of 35% obtained for **32**, can be regarded as satisfactory considering that a trans/anti/trans-fused tricyclic skeleton, containing six stereogenic centers and an exocyclic double bond, was selectively formed among more than 190 potential regio- and stereoisomers.[14]

As we expected, the aromatic subunits remained unchanged after radical cyclization in all the products obtained, including the strongly activated aromatic rings

TABLE 1. Products, Yields, and Reaction Times in the Synthesis of Compounds 15−23

Carbonate	Stannane	Coupling product	Yield	Time
14b	 **10a**	**15**	(92 %)	48 h
14b	 **10b**	**16**	(66 %)	48 h
14b	 **10c**	**17**	(68 %)	48 h
14b	 **10d**	**18**	(70 %)[b]	48 h
14b	 **10e**	**19**	(67 %)[a]	72 h
14b	 **10f**	**20**	(66 %)	72 h
14a	 **10a**	**21**	(77 %)[b]	51 h
14a	 **10e**	**22**	(68 %)[a]	120 h
14c	 **10a**	**23**	(66 %)	50 h

[a] LiCl (3 mol) was added. [b] Performed with 10 mol % $Pd(dba)_2$ instead of the normal 2 mol %.

of substrates **19** and **22**. This represents a significant difference, not only with regard to carbocationic processes but also in contrast with radical cyclizations promoted by other transition metals.[15,16] In fact, this cyclization proceeds in a regio- and stereoselective fashion and the intermediates involved are inert to benzene rings with different substitution patterns, including activating and deactivating groups with various steric demands. Thus, our procedure has allowed us to synthesize, for example, the zonarol-related structure **31** (which could then be easily transformed in meroterpenoids **2**−**5**) in only four

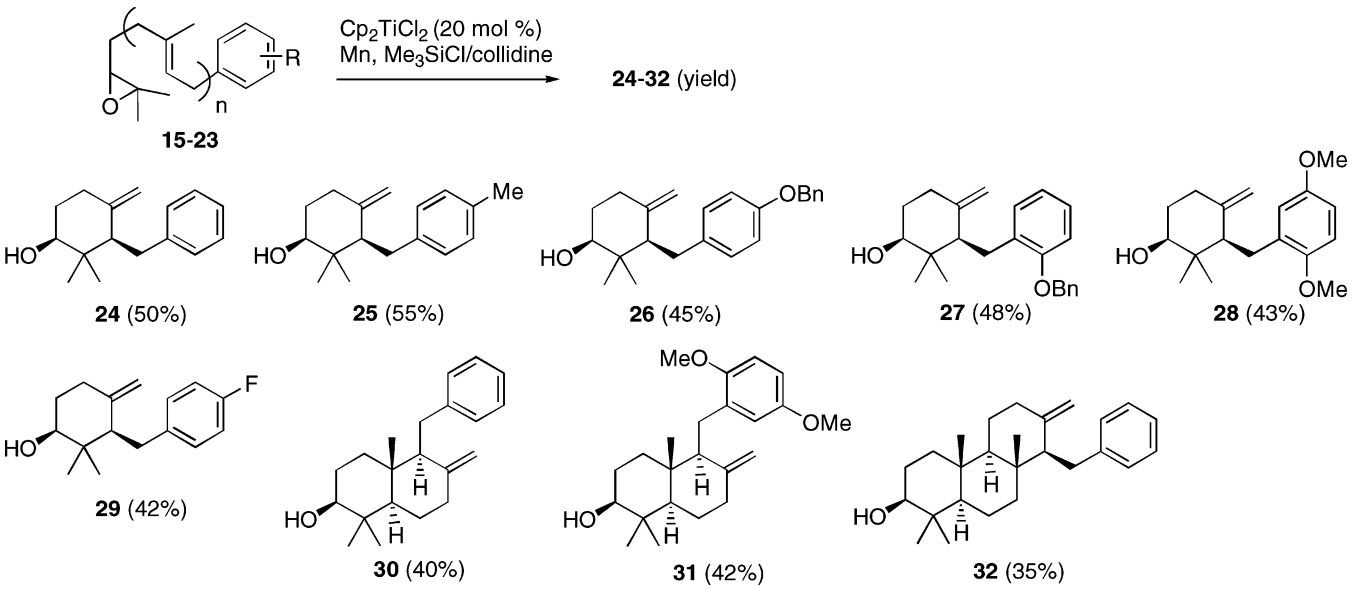
(13) Products **15**−**23** retained the (*E*)-configuration of the double bonds unchanged after coupling reaction.

(14) It should be noted that carbocationic sequential cyclizations towards simpler trans/anti/trans-fused tricyclic terpenoids gave yields lower than 10%; see: vanTamelen, E. E.; Nadeau, R. C. *J. Am. Chem. Soc.* **1967**, *89*, 176.

(15) (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (b) Snider, B. B.; Mohan, R.; Kates, S. A. *Tetrahedron Lett.* **1987**, *28*, 841.

(16) Similar results have been observed in PET-induced cyclizations: Rosales, V.; Zambrano, J.; Demuth, M. *Eur. J. Org. Chem.* **2004**, 1798.

SCHEME 4. Titanocene-Catalyzed Cyclization of 15−23.



steps with an overall yield of 16%. The method also proved to be useful in the synthesis of other types of meroterpenoid-related structures, including those containing a mono- (**24**−**29**) or a diterpenoid moiety (**32**).

In summary, we describe here a novel approach for synthesizing polycyclic fungal and marine meroterpenoids based on the Stille-type coupling of aryl stannanes and allylic carbonates followed by the titanocene-catalyzed domino cyclization of the corresponding aryl epoxypolyprenes. This strategy has proved useful in the synthesis of several meroterpenoid-related structures (**24**−**32**) containing a mono-, sesqui-, or diterpenoid moiety and a nonfused aromatic subunit with different substitution patterns. Moreover, as the Stille coupling under Echavarren's conditions proved to be compatible with preformed epoxides, the method might presumably be extended to the enantioselective preparation of bioactive meroterpenoids, starting with enantiomerically enriched epoxypolyprenols obtained from commercial **12a**−**c** with the aid of the Noe−Lin catalyst,[17] a task we are currently engaged in.

Experimental Section

Model Procedure for the Synthesis of Allylic Carbonates. Diethyl carbonate (20 mmol) was added to a mixture of epoxypolyprenols **13a**−**c** (1 mmol) and NaH (4 mmol) in THF (20 mL) at room temperature. The reaction was then stirred for 4 h; the solvent was removed, and the residue was submitted to flash chromatography (hexanes−EtOAc, 20:1) obtaining the corresponding epoxyprenyl ethyl carbonates **14a** (100%), **14b** (100%), and **14c** (63%).

Model Procedure for the Synthesis of Aryltributylstannanes (10). *t*-BuLi (2.2 mmol) was added to a solution of the corresponding bromoderivative (1 mmol) in THF (10 mL) at −78 °C, and the reaction was stirred for 30 min. Bu_3SnCl (1.1 mmol) was then added and the resulting mixture stirred at room temperature for 7 h. The reaction was then diluted with *t*-BuOMe, washed with saturated $NaHCO_3$, and dried over anhydrous Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (hexanes−EtOAc), affording the expected arylstannanes.

Model Procedure for Stille Coupling. A mixture of carbonate **14a**−**c** (1 mmol), arylstannane (1.1 mmol), $Pd(dba)_2$ (0.02 mmol), and water (2 mmol) in DMF (3 mL) was stirred at room temperature for several hours (see Table 1). The reaction was then diluted with *t*-BuOMe, washed with saturated $NaHCO_3$, and dried over anhydrous Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (hexanes−EtOAc), giving the expected coupling products **15**−**22**.

Model Procedure for Radical Cyclization. Strictly deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (0.5 mmol) and Mn dust (20 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of epoxide (2.5 mmol), 2,4,6-collidine (20 mmol), and Me_3SiCl (10 mmol) in THF (2 mL) was added, and the mixture was stirred for 16 h. The reaction was then quenched with 2 N HCl and extracted with *t*-BuOMe. The organic layer was washed with brine and dried (anhydrous Na_2SO_4) and the solvent removed. The residue was solved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h. The mixture was then diluted with *t*-BuOMe, washed with brine, and dried (anhyd Na_2SO_4) and the solvent removed. Products obtained were isolated by flash chromatography of the residue (hexane/*t*-BuOMe). Besides exocyclic alkenes **24**−**32**, minor proportions of endocyclic regioisomers were detected.

Acknowledgment. The authors thank the Spanish DGICYT (Projects PB 98-1365 and BQ2002-032M) and the "Junta de Andalucía" (PAI group FQM339) for their financial support. J.J. thanks the Spanish Ministry of Science and Technology for a predoctoral grant. Thanks are given to Dr. A. F. Barrero for his collaboration in the early stage of this work. We thank our English colleague Dr. J. Trout for revising our text.

Supporting Information Available: Spectroscopic data and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049253R

(17) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741. (b) Corey, E. J.; Luo, G.; Lin, S. *J. Am. Chem. Soc.* **1997**, *119*, 9927.