A Highly Effective One-Pot Bicycloannulation Methodology for the Synthesis of Berban and Yohimban Systems Based on Organotin-Mediated Three-Component Coupling (N-Acylative Pentadienylation of C=N Bonds)

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A highly effective bicycloannulation methodology for the synthesis of berban and yohimban alkaloid systems is described. Three-component coupling reactions of 2,4-pentadienyltin reagents with C=N bonds and α,β-unsaturated acyl chlorides furnish bicycloannulated products in a one-pot operation. For example, the reactions of 2,4-pentadienyltributyltin (1) with isoquinoline derivatives activated by acryloyl chloride afford the tetracyclic (±)-*allo*-berban systems stereoselectively. Similarly, the reaction of 1 with 3,4-dihydro-β-carboline (11) gives the pentacyclic (±)-*allo*-yohimban system. The reaction is not affected by the stereochemistry of the 2,4-pentadienyltin reagent. A new substituted 2,4-pentadienyltin reagent, 3-(hydroxymethyl)-2,4-pentadienyltrimethyltin (19), is prepared via 3-(hydroxymethyl)pentadienyl dianion. The three-component coupling reaction of 19 with 11 and acryloyl chloride affords the (±)-*allo*-16-(hydroxymethyl)yohimban system, from which (±)-nitraraine is readily synthesized. In addition, 1,3-asymmetric induction leads to the high diastereoselectivity realized in bicycloannulation (up to 94% de) when (*S*)-3-[(*tert*-butyldimethylsiloxy)methyl]-3,4-dihydroisoquinoline (27), which is readily derived from L-phenylalanine, is used in the three-component coupling reaction.

The development of synthetic methods for tetracyclic protoberberine-type and pentacyclic yohimbine-type alkaloids has attracted much attention for some decades.[2,3] In an example of the use of intramolecular Diels–Alder reactions in synthesis of complex polycyclic framework,[4] Martin recently used such an approach for constructing yohimbine-type alkaloids.[5] Concurrently, we reported that some organotin reagents react chemoselectively with C=N bonds in cyclic systems activated by acyl chlorides. This chemoselective reaction provides an effective method for the introduction of several kinds of unsaturated carbon substituents into nitrogen heterocycles.[6] Taking these organotin-mediated N-acylative α-addition reactions and the efficiency of the intramolecular Diels–Alder approach to the synthesis of polycyclic compounds into consideration, we recently found that simultaneous 1,2-introduction of allylic and $\alpha,\beta,\gamma,\delta$-unsaturated acyl groups into the isoquinoline system can be accomplished by means of organotin reagents and that the subsequent inverse electron demand intramolecular Diels–Alder reactions give pseudoberban systems stereoselectively.[7-9]

In a logical extension of the above sequences, which use inverse electron demand Diels–Alder reactions, we have studied an attractive approach to these alkaloids that utilizes *normal electron demand* intramolecular Diels–Alder cycloadditions. We anticipated that the normal cycloaddition might proceed more easily than the inverse one and that the stereochemical consequences of the former might be different from those of the latter.[5a,10] Furthermore, the double bond resulting from the former reaction is located at the δ,ϵ-positions, whereas it is at the β,γ-positions in the latter. A highly effective method for 1,2-addition of 2,4-pentadienyl and α,β-unsaturated acyl groups into a C=N bond was critical for effecting the normal cycloaddition. We considered the three-component coupling reaction of a C=N bond with a 2,4-pentadienyltin reagent and acryloyl chloride to be the most straightforward tool for the present approach (Scheme I).

(1) (a) Faculty of Integrated Human Studies. (b) Faculty of Engineering.

(2) For a recent review: Bhakuni, D. S.; Jain, S. In *Protoberberine Alkaloids*; Brossi, A. Ed.; Academic Press: New York, 1986; p 95.

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(6) (a) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1985**, *50*, 287. (b) Yamaguchi, R.; Moriyasu, M.; Kawanisi, M. *Tetrahedron Lett.* **1986**, *27*, 211. (c) Yamaguchi, R.; Moriyasu, M.; Takase, I.; Kawanisi, M.; Kozima, S. *Chem. Lett.* **1987**, 1519. (d) Yamaguchi, R.; Hata, E.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1785. (e) Yamaguchi, R.; Hamasaki, T.; Utimoto, K. *Chem. Lett.* **1988**, 913. (f) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1988**, *53*, 3507.

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(8) Yamaguchi, R.; Otsuji, A.; Utimoto, K.; Kozima, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 298.

(9) For analogous 1,2-additions to C=N bonds by means of organosilicon reagents and subsequent intramolecular hetero and inverse electron demand Diels–Alder reactions, see: (a) Martin, S. F.; Benage, B.; Hunter, J. *J. Am. Chem. Soc.* **1988**, *110*, 5925. (b) Martin, S. F.; Geraci, L. S. *Tetrahedron Lett.* **1988**, *29*, 6725. (c) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161.

(10) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976; p 86.

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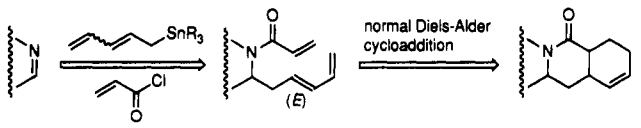
Scheme I

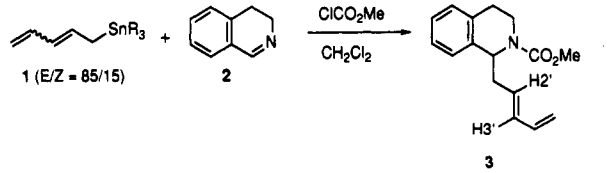


Although the bicycloannulation methodology shown in Scheme I looked attractive, the following points were crucial to the success of the sequence: the substitution had to take place at either of the terminal carbons (ϵ or α) of 2,4-pentadienyltin, and the resulting 2,4-pentadienyl moiety had to retain the favorable *E* configuration for the subsequent intramolecular Diels–Alder cycloaddition.[11] Since Seyferth has prepared 2,4-pentadienyltins, reactions of the reagents with several nucleophiles have been explored.[12,13] Naruta and Maruyama have extensively investigated Lewis acid-promoted reactions of 2,4-pentadienyltin reagents with quinones and have utilized the reactions for synthesis of anthracyclins.[14] To the best of our knowledge, however, there has been no report of the reactions of 2,4-pentadienyltin reagents with iminium salts.[15] We report here (1) a highly effective one-pot bicycloannulation methodology for the synthesis of berban and yohimban systems through three-component coupling of 2,4-pentadienyltin reagents with cyclic imines and an α,β-unsaturated acyl chloride,[16] (2) a preparation of a new 3-substituted 2,4-pentadienyltin reagent, 3-(hydroxymethyl)-2,4-pentadienyltrimethyltin and its use for a short synthesis of (±)-nitraraine,[17] and (3) a highly diastereoselective bicycloannulation through 1,3-asymmetric induction of chiral imines.

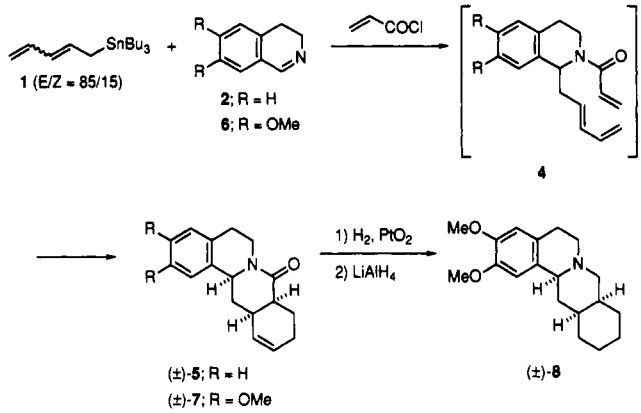
Results and Discussion

Synthesis of (±)-*allo*-Berban Systems. Previously, we reported that some organotin reagents (allyl-, allenyl-, alkynyl-, and benzyltins) readily react with C=N bonds activated by chloroformate esters. The reaction provides a valuable method for the introduction of some useful carbon substituents into nitrogen heterocycles.[6] Thus, we first examined a reaction of 2,4-pentadienyltributyltin (1) with 3,4-dihydroisoquinoline (2) activated by methyl chloroformate. Since it is difficult to prepare pure (*E*)- or (*Z*)-2,4-pentadienyltributyltin stereoselectively,[18] a stereoisomeric mixture was used. When methyl chloroformate was added to a solution of an 85:15 mixture of (*E*)- and (*Z*)-1 and 2 in CH_2Cl_2, the addition reaction proceeded smoothly to give 2-(methoxycarbonyl)-1-[(*E*)-2,4-pentadienyl]-3,4-dihydroisoquinoline (3) as the only isolated product in 88% yield. The *E* configuration of the double bond was determined by the large coupling constant of 15 Hz between H2′ (δ 5.66) and H3′ (δ 6.02) in the ^{1}H NMR spectrum of 3 (Scheme II). As will be discussed later, we have found that, irrespective of the stereochemistry of 2,4-pentadienyltin reagent, the 2,4-pentadienyl substituent introduced has the *E* configuration.

Scheme II



Scheme III



Since the above result indicated that the reaction of a 2,4-pentadienyltin reagent with a *N*-acyliminium salt had taken place in a favorable manner for the subsequent Diels–Alder reaction to occur, we next examined the three-component coupling reaction of a C=N bond with a 2,4-pentadienyltin and an α,β-unsaturated acyl chloride. When acryloyl chloride was added to 1 (*E*/*Z* = 85/15) and 3,4-dihydroisoquinoline (2), the reaction proceeded cleanly to give tetracyclic derivative 5 as the only isolated product in 83% yield. That bicycloannulated product 5 was obtained directly instead of 1,2-adduct 4 indicated that the normal electron demand intramolecular Diels–Alder reaction had taken place *even at room temperature* (Scheme III). Similarly, the reaction of 6,7-dimethoxy-3,4-dihydrosioquinoline (6) with 1 and acryloyl chloride afforded bicycloannulated product 7 in 81% yield in a one-pot operation. The structures of tetracyclic products 5 and 7 were elucidated by NMR analyses.[19,20] Furthermore, the transformation of 7 to the known (±)-*allo*-7,8-

(11) In general, the (*E*)-2,4-pentadienyl system can easily attain the favorable s-cis conformation for the cycloaddition, but the (*Z*)-2,4-pentadienyl system cannot. See: Carruthers, W. *Some Modern Methods of Organic Synthesis*; Cambridge University Press: Cambridge, 1986; p 199.

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(14) (a) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *J. Org. Chem.* **1988**, *53*, 1192. (b) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *J. Chem. Soc. Perkin Trans. 1* **1991**, 831.

(15) For reactions of allylic tin reagents with iminium salts, see: (a) Borg, R. M.; Mariano, P. S. *Tetrahedron Lett.* **1986**, *27*, 2821. (b) Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 1378. For Lewis acid-promoted reactions of allylic tin reagents with aldimines and *N*-acyliminium salts, see: (c) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146. (d) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115. (e) Martel, A.; Daris, J.-P.; Bachand, C.; Menard, M.; Durst, T.; Belleau, B. *Can. J. Chem.* **1983**, *61*, 1899. (f) Fujimoto, K.; Iwao, Y.; Hirai, K. *Tetrahedron Lett.* **1985**, *26*, 89. (g) Fliri, H.; Mak, C.-P. *J. Org. Chem.* **1985**, *50*, 3438. (h) Yamamoto, Y.; Schmid, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1310. (i) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345. For reactions of aryl- and alkynyltin reagents with iminium salts, see: (j) Cooper, M. S.; Heaney, H. *Tetrahedron Lett.* **1986**, *27*, 5011. (k) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501.

(16) For a preliminary report, see: Yamaguchi, R.; Hamasaki, T.; Utimoto, K.; Kozima, S.; Takaya, H. *Chem. Lett.* **1990**, 2161.

(17) For a preliminary report, see: Yamaguchi, R.; Hamasaki, T.; Sasaki, T.; Kozima, S.; Takaya, H. *Synlett* **1991**, 719.

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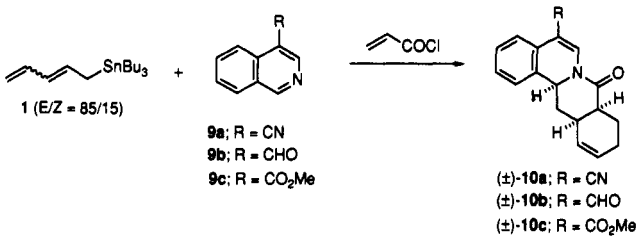
Scheme IV



dimethoxyberban (8)[21] confirmed the structure of 7. Thus, this three-component coupling reaction provides a new, short, and stereoselective method for the synthesis of *allo*-berban systems. It should also be noted that the stereochemistry of the bicycloannulated produts is complementary to that obtained from the inverse electron demand Diels–Alder reactions, where pseudoberban systems are the major products.[7]

As shown in Scheme IV, some functional groups on the isoquinoline can be tolerated in the three-component coupling reaction. 4-Cyano-, 4-formyl-, and 4-(methoxycarbonyl)isoquinolines (**9a–c**) were readily converted to bicycloannulated tetracyclic products **10a–c** in 81%, 66%, and 64% yields, respectively, in one-pot operations. The high chemoselectivity of the reaction may be valuable for the synthesis of the berban systems containing functionality.

As mentioned before, it is rather difficult to obtain stereochemically pure 2,4-pentadienyltin reagent; therefore, we used an 85:15 mixture of (*E*)- and (*Z*)-**1** in the reactions. Hence, it is necessary that the influence of the stereochemistry of the tin reagent on the reaction be determined, since it has been reported that the Lewis acid-promoted reactions of 2,4-pentadienyltins with quinones are greatly dependent on the stereochemistry of the tin reagents.[14a,18b] A 25:75 mixture of (*E*)- and (*Z*)-**1** was prepared from the pentadienyl anion generated by treatment of 1,4-pentadiene with *n*-BuLi–*t*-BuOK.[22] When methyl chloroformate was added to a solution of **1** (*E*/*Z* = 25/75) and **2** in CH_2Cl_2, addition product **3** was obtained in 79% yield (Scheme V). Furthermore, the three-component coupling reaction of **1** (*E*/*Z* = 25/75) with **2** and acryloyl chloride afforded tetracyclic product **5** in 77% yield. These results clearly showed that reactions of **1** with *N*-acyliminium salts give rise to an (*E*)-2,4-pentadienyl group irrespective of the stereochemistry of **1**.

On the basis of the above experimental results, we propose the pathway shown in Chart I for the bicycloannulation reactions. It is highly probable that the initial attack of **1** on the *N*-acyliminium salt takes place at the ϵ-position of **1** to produce π-allylic carbocation intermedites

Scheme V

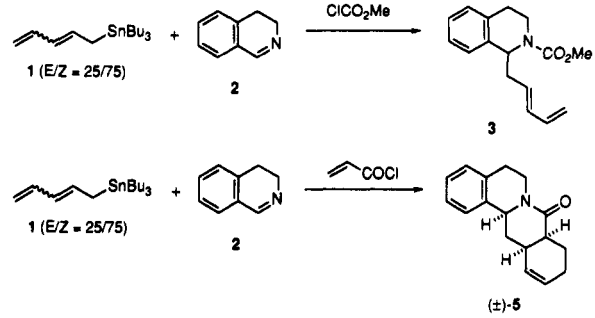
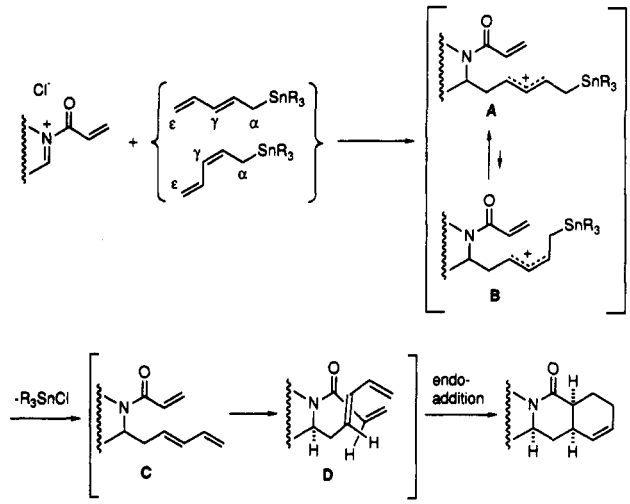


Chart I



A and **B**, either of which, on destannylation, can give rise to (*E*)-2,4-pentadienyl-substituted product **C**.[23] The (*E*)-stereospecificity of the addition reaction is very advantageous because preparation of stereochemically pure 2,4-pentadienyltin reagents is not usually easy. Subsequently, the intramolecular cycloaddition of an equatorial 2,4-pentadienyl group to an equatorial acryloyl group occurs exclusively in the endo-fashion (**D**) to afford the allo-stereoisomer; this mode of cycloaddition is in marked contrast to the exo-mode observed in the inverse electron demand cycloadditions.[7] Thus, the high stereoselectivity of the bicycloannulation reactions can be ascribed to the (*E*)-stereospecificity of the nucleophilic addition step and to the high endo-selectivity of the cycloaddition step.

Synthesis of (±)-*allo*-Yohimban and (±)-Nitraraine. The present methodology is also applicable to the synthesis of the yohimban system, a basic skeleton of one of the most studied and physiologically interesting alkaloids.[3] The three-component coupling reaction of 3,4-dihydro-β-carboline (**11**) and **1** and acryloyl chloride afforded directly pentacyclic yohimban derivative **12** in 54% yield (Scheme VI). The yield increased to 66% when the reaction mixture was heated at reflux after benzene had been added. Thus, the DE ring of the yohimban system can be added to the ABC ring stereoselectively in a one-flask operation.[9c] Catalytic reduction of **12** followed by hydride reduction furnished (±)-*allo*-yohimban (**13**).[24]

(19) There are two possible modes of addition for the intramolecular Diels–Alder cycloadditions: endo-addition of the acryloyl group to the 2,4-pentadienyl group should produce the allo-stereoisomer, and exo-addition should produce the pseudo-stereoisomer. The ^1H NMR spectra of **5** and **7** show that H1 appears as doublet of doublets (δ 4.73, J = 4.3, 11.6 Hz and δ 4.66, J = 4.3, 11.6 Hz, respectively), whereas we have observed that H1 of the pseudoberban system appears as triplet.[7,20]

(20) Uskokovi'c, M.; Bruderer, H.; Planta, C. v.; Williams, T.; Brossi, A. *J. Am. Chem. Soc.* **1964**, *86*, 3364.

(21) For synthesis of berban derivatives and their physiological activities, see: (a) Szabó, L.; Honty, K.; Töke, L.; Tóth, I.; Szántay, C. *Chem. Ber.* **1972**, *105*, 3215. (b) Szabó, L.; Honty, K.; Töke, L.; Szántay, C. *Chem. Ber.* **1972**, *105*, 3231. (c) Tóth, I.; Szabó, L.; Bozsár, G.; Szántay, C.; Szekeres, L.; Papp, J. G. *J. Med. Chem.* **1984**, *27*, 1411. (d) Tóth, I.; Bozsár, G.; Szabó, L.; Baitz-Gács, E.; Szántay, Cs. *Liebigs Ann. Chem.* **1987**, 243.

(22) Schlosser, M.; Rauchschwabe, G. *J. Am. Chem. Soc.* **1978**, *100*, 3258.

(23) In the Lewis acid-promoted reactions of 2,4-pentadienyltin reagents with carbonyl compounds, exclusive ϵ-selectivity has generally been observed, although γ-selectivity has been reported in a few cases.[13,14] See also ref 12c.

(24) (a) Wenkert, E.; Chang, C.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orita, K. *J. Am. Chem. Soc.* **1976**, *98*, 3654. (b) Lounasmaa, M.; Jokela, R. *Tetrahedron* **1990**, *46*, 615.

Scheme VI

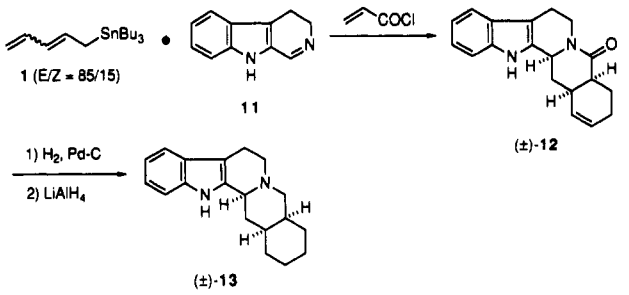
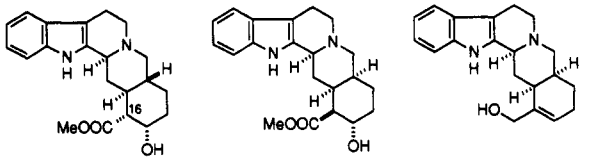
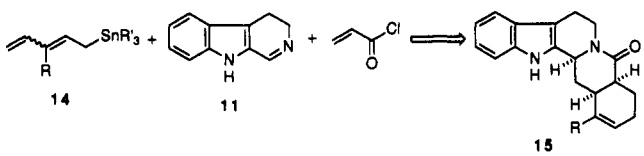


Chart II



Yohimbine Rauwolscine (α-Yohimbine) Nitraraine

Scheme VII

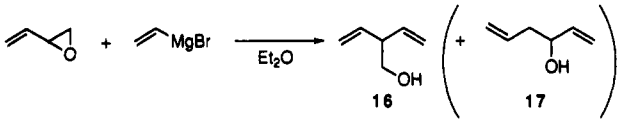


Considering that most of the yohimban alkaloids possess a one-carbon functionality at the C16 position in the E ring (Chart II), it seemed attractive to prepare a 2,4-pentadienyltin reagent that contained an appropriate one-carbon unit at the C3 position because the three-component coupling of 11 with 3-substituted 2,4-pentadienyltin reagent 14 and acryloyl chloride could provide an effective route to 16-substituted *allo*-yohimban system 15 (Scheme VII). We chose a novel α-yohimban alkaloid, nitraraine,[25,26] as a target molecule. Thus, it was necessary to prepare a 3-(hydroxymethyl)-2,4-pentadienyltin reagent (14, R = CH_2OH), since very few substituted 2,4-pentadienyltin reagents had been reported.[27]

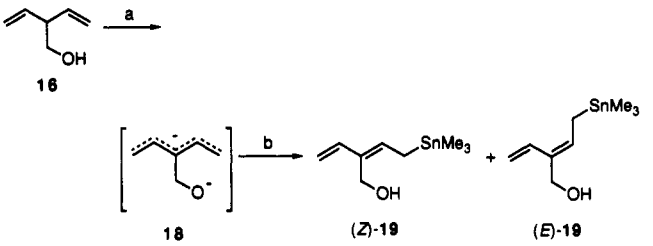
We first pursued a conventional method for the preparation of 3-(hydroxymethyl)-1,4-pentadiene (16, 2-vinyl-3-butenol) as a suitable precursor of 14 (R = CH_2OH). Although it had been reported[28] that the reaction of butadiene monoepoxide with vinylmagnesium bromide in either gave a 5:4 mixture of 16 and 3-hydroxy-1,5-hexadiene (17) as a result of nonregioselective attack of vinylmagnesium bromide on the epoxide, we found that the use of 2–3 equiv of vinylmagnesium bromide greatly improved the regioselectivity to afford 16 with 92–94% selectivity[29,30] (Scheme VIII).

Having the desired alcohol 16 in hand, we next examined a preparation of a 3-(hydroxymethyl)-2,4-pentadienyltin

Scheme VIII



Scheme IX[a]



[a] Key: (a) *n*-BuLi, TMEDA, −70 to 0 °C; (b) Me_3SnCl, then H_2O.

Table I. Reactions of Dianion 18 with Trimethyltin Chloride

					19	
run	equiv of Me_3SnCl	solvent	temp (°C)	time[a] (min)	yield[b] (%)	Z/E[c]
1	2	THF	−70 to 0	90 (30)	39	84/16
2	2	DME	−70 to 0	100 (60)	46	87/13
3	2	ether(DME)	−70 to 0	90 (30)	48	96/4
4	1	ether(DME)	−70 to 0	80 (30)	41	98/2
5	2	THF	0	(60)	37	25/75
6	2	DME	0	(30)	49	30/70
7	2	ether(DME)	0	(60)	47	89/11

[a] Reaction time at 0 °C is shown in parentheses. [b] Isolated yield. [c] Determined by ^1H NMR.

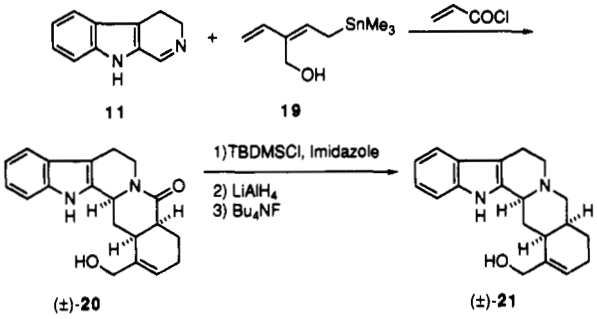
reagent. The first attempt to prepare 3-(methoxymethyl)-2,4-pentadienyltin via 3-(methoxymethyl)pentadienyl monoanion generated from methyl ether of 16 with *n*-BuLi failed, probably because of demethoxylation in the monoanion.[31] We found, however, that dianion 18, generated from 16, could be trapped by trimethyltin chloride to afford 3-(hydroxymethyl)-2,4-pentadienyltrimethyltin (19) as a mixture of *Z*/*E* stereoisomers in modest yields (Scheme IX). The results are summarized in Table I.

3-(Hydroxymethyl)pentadienyl dianion (18), which was generated by treatment of 16 with 2.0–2.5 equiv of *n*-BuLi in the presence of TMEDA at −70 to 0 °C, was allowed to react with 1–2 equiv of trimethyltin chloride at the temperature indicated in Table I. When trimethyltin chloride was added to the dianion 18 below −70 °C, the (*Z*)-isomer [(*Z*)-19] was produced predominantly over the (*E*)-isomer [(*E*)-19], and very high stereoselectivity (96–98%) was observed when ether containing a small amount of DME was used as the solvent (runs 1–4).[32] In contrast, the (*E*)-isomer was produced preferentially when trimethyltin chloride was added at 0 °C in THF or DME (runs 5, 6).[33]

The three-component coupling reaction of 19 with 11 and acryloyl chloride was successfully conducted without protection of the hydroxyl group of tin reagent 19 to furnish directly pentacyclic (±)-*allo*-16-(hydroxymethyl)yohim-

(25) Ibragimov, A. A.; Yunusov, S. Y. *Khim. Prir. Soed.* **1985**, *536*; *Chem. Abstr.* **1986**, *104*, 183259Z.
(26) For asymmetric synthesis of (−)-21, see: Takano, S.; Samizu, K.; Sugihara, T.; Satoh, S.; Ogasawara, K. *Chem. Lett.* **1989**, 1777.
(27) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *J. Org. Chem.* **1991**, *56*, 2011.
(28) Ent, H.; Koning, H.; Speckamp. W. N. *Tetrahedron Lett.* **1985**, *26*, 5105.
(29) Although the origin of the high regioselectivity is not yet clear, the Lewis acidity of excess vinyl Grignard reagent might play a role.
(30) In the reactions of aryl Grignard reagents with butadiene monoepoxide in ether, the predominant formation of 2-aryl-3-butenols has been reported. See: (a) Rose, C. B.; Smith, C. W., Jr. *J. Chem. Soc., Chem. Commun.* **1969**, 428. (b) Ent, H.; Konig, H. d.; Speckamp, W. N. *J. Org. Chem.* **1986**, *50*, 1687.
(31) For recent reviews on pentadienyl monoanions, see: (a) Yasuda, H.; Nakamura, A. *J. Organomet. Chem.* **1985**, *285*, 15. (b) Ernst, R. D. *Acc. Chem. Res.* **1985**, *18*, 56. See also ref 27 and references cited therein.
(32) The (*Z*)-isomer may be produced from the W-form of 18.
(33) The (*E*)-isomer may be produced from the U- or S-form of 18. The reason for the reversal of the stereochemistry is now under investigation.

Scheme X



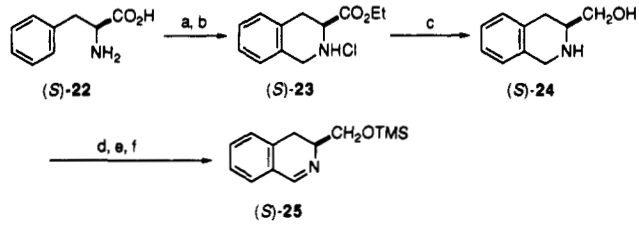
ban derivative **20** in 54% yield (Scheme X). The yield went up to 63% when the reaction mixture was heated at reflux after benzene had been added. Eventually, protection of the hydroxyl group of **20** followed by hydride reduction and deprotection afforded (±)-nitraraine [(±)-**21**] in 57% overall yield. The ^{1}H NMR spectrum (400 MHz) of (±)-**21** was essentially identical with that (500 MHz) of authentic (−)-**21**.[26]

Diastereoselective Bicycloannulation through 1,3-Asymmetric Induction. The present bicycloannulation reaction proved to be highly stereoselective with respect to the relative stereochemistry of the resulting two rings. Hence, it was expected that an asymmetric introduction of a 2,4-pentadienyl moiety would result in an asymmetric bicycloannulation. In keeping with the expectation, Meyers recently reported that an asymmetric introduction of a 2,4-pentadienyl moiety using chiral formamidines and the subsequent introduction of acryloyl moiety produced *allo*-yohimban systems in high enantiomeric excess.[34] In our methodology, we planned to utilize diastereoselective addition of a 2,4-pentadienyltin reagent to an appropriate chiral *N*-acyliminium salt through 1,3-asymmetric induction[35] and to prepare a chiral 3-substituted 3,4-dihydroisoquinoline from L-phenylalanine (**22**).

We first prepared chiral 3-(hydroxymethyl)-3,4-dihydroisoquinoline derivatives from **22** according to the literature procedures used for the preparation of the racemic derivatives.[36] Thus, (*S*)-**22** was converted to (*S*)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline (**24**) in three steps. The enantiomeric excess was determined to be 98% by a HPLC analysis using a chiral column. Trimethylsilylation of (*S*)-**24** followed by N-chlorination, dehydrochlorination, and retrimethylsilylation gave (*S*)-3-[(trimethylsiloxy)methyl]-3,4-dihydroisoquinoline (**25**) (Scheme XI).

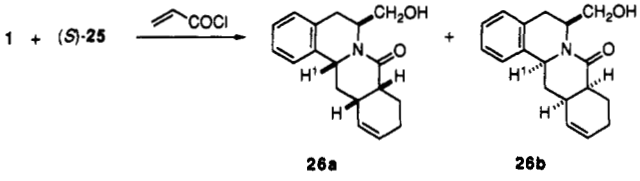
The three-component coupling reaction of chiral substrate (*S*)-**25** with **1** and acryloyl chloride was conducted in the usual manner to afford two bicycloannulated tetracyclic diastereomers **26a** and **26b** in 79% total yield (Scheme XII). The ratio of **26a** to **26b** was 88:12 (76% de). The structures of **26a** and **26b** were elucidated by ^{1}H NMR NOE measurements: irradiation of the methylene protons of the hydroxymethyl group enhanced the signal due to H1 of **26a** by 3.9%, and no NOE was observed with **26b**. Furthermore, the structure of **26a** was unambiguously

Scheme XI[a]

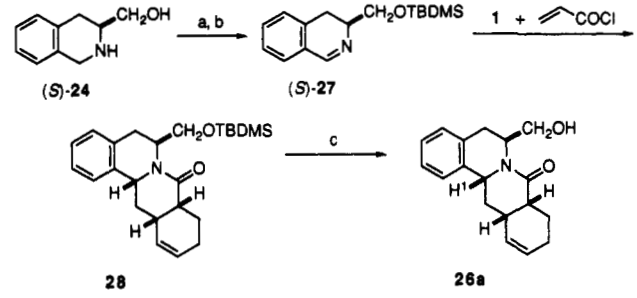


[a] Reagents and conditions: (a) aqueous HCHO, HCl, 97 °C; (b) EtOH, $SOCl_2$; (c) $LiAlH_4$, Et_2O; (d) TMSCl, Et_3N, THF; (e) NCS, CH_2Cl_2, then 20% aqueous KOH, Bu_4NI; (f) TMSCl, Et_3N, THF.

Scheme XII



Scheme XIII[a]



[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF; (b) NCS, CH_2Cl_2 then 30% aqueous KOH, Bu_4NI; (c) Bu_4NF, THF.

determined by single-crystal X-ray analysis. The diastereoselectivity suggests that the nucleophilic attack of the 2,4-pentadienyltin reagent on the *N*-acyliminium salt takes place preferentially from the axial direction, which is anti to the bulky (trimethylsiloxy)methyl group. We next examined a more bulky substituent, a *tert*-butyldimethylsilyl group.

(*S*)-3-[(*tert*-Butyldimethylsiloxy)methyl]-3,4-dihydroisoquinoline (**27**) was prepared from (*S*)-**24** in the conventional manner.[36c] The three-component coupling reaction of (*S*)-**27** with **1** and acryloyl chloride proceeded more slowly (0 °C for 2 h and then 15–20 °C for 46 h) than that of (*S*)-**25** (0 °C for 2 h and then 15–20 °C for 21 h) to afford an inseparable mixture of bicycloannulated tetracyclic product **28** and its diastereomer in 82% yield (Scheme XIII). Desilylation of the mixture with tetrabutylammonium fluoride gave tetracyclic alcohol **26a** along with a very small amount of its diastereomer **26b**. Inspection of the crude mixture by HPLC showed that the ratio of **26a** and **26b** was 97:3, i.e., 94% de, a much higher diastereomeric excess than that with trimethylsiloxy derivative (*S*)-**25**. Keeping the reaction at 0 °C for a longer period (0 °C for 77 h and 15–20 °C for 22 h) did not improve the diastereomeric excess (94% de) but did lower the yield (57%). This result indicates that the addition reaction takes place at or near rt. A similar three-component coupling reaction of racemic (±)-**27** with **1** and acryloyl chloride followed by desilylation gave racemic (±)-**26a** in 92% de. It is interesting that very high diastereoselectivity (92–94%), resulting from 1,3-asymmetric induction, is obtained when the reaction

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(35) For recent examples, see: (a) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. (b) Shono, T.; Fujita, T.; Matsumura, Y. *Chem. Lett.* **1991**, 81.

(36) (a) Archer, S. *J. Org. Chem.* **1951**, *16*, 430. (b) Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2115. (c) Cho, I.-S.; Chang, S. S. S.; Ho, C.; Lee, C.-P.; Ammon, H. L.; Mariano, P. S. *Heterocycles* **1991**, *32*, 2161.

is allowed to proceed at rt (15–20 °C).[37] The enantiomeric excess of **26a** was determined to be 94% by ^{19}F NMR analysis of its MTPA ester.

In conclusion, we have demonstrated the effectiveness of bicycloannulation methodology that uses organotin-mediated three-component coupling reactions of the C=N bond of cyclic imines with 2,4-pentadienyltin reagents and acryloyl chloride followed by spontaneous intramolecular Diels–Alder cycloadditions. By this methodology, *allo*-berban and *allo*-yohimban systems can be stereoselectively constructed in one-pot operations. The utilization of a newly prepared organotin reagent, 3-(hydroxymethyl)-2,4-pentadienyltrimethyltin, makes it possible to directly elaborate the *allo*-16-(hydroxymethyl)yohimban framework, from which (±)-nitraraine is readily synthesized. In addition, 1,3-asymmetric induction leads to a diastereoselective bicycloannulation (up to 94% de) of chiral imines to furnish chiral *allo*-berban systems in high enantiomeric purity.

Experimental Section

Methods and Materials. All reactions involving air- and moisture-sensitive reagents were performed under an inert atmosphere of argon. Melting points were measured with a hot stage apparatus and are uncorrected. ^1H NMR spectra were recorded at 200, 270, or 400 MHz. Characteristic ^1H NMR data are shown. ^{13}C NMR spectra were recorded at 22.5 or 67.5 MHz. ^{119}Sn NMR spectra wee recorded at 33 MHz. Column chromatography was carried out with Wako-gel C-200. The following compounds were prepared according to the literature procedures: 2,4-pentadienyltributyltin (**1**),[12] 3,4-dihydroisoquinoline (**2**),[38] 6,7-dimethoxy-3,4-dihydroisoquinoline (**6**),[39] 4-cyano-, 4-formyl-, and 4-(methoxycarbonyl)isoquinolines (**9a–c**),[40,41] and 3,4-dihydro-β-carboline (**11**).[42] Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and diethyl ether were distilled over sodium–benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5 before use. Benzene (C_6H_6) and dimethylformamide (DMF) were distilled from CaH_2. Elemental analyses were performed by Kyoto University Microanalysis Center.

General Procedures for Three-Component Coupling Reactions. To an ice-cooled solution of a imine (1.0 mmol) and a 2,4-pentadienyltin reagent (1.0 mmol) in CH_2Cl_2 (5–7 mL) was added an acyl chloride (1.2–1.3 mmol). The reaction mixture was stirred at 0 °C for 2 h and then at rt until the starting materials disappeared (the reaction was monitored by TLC). The solvent was evaporated, and the residue was chromatographed on silca gel. Elution by hexane–CH_2Cl_2 or hexane–AcOEt gave the product(s). An 85:15 mixture of (*E*)- and (*Z*)-**1** was used unless otherwise noted.

2-(Methoxycarbonyl)-1-[(*E*)-2,4-pentadienyl]-1,2,3,4-tetrahydroisoquinoline (3). The reaction of **1** (749 mg; 2.1 mmol) with **2** (266 mg; 2.0 mmol) and $ClCO_2Me$ (0.20 mL; 2.6 mmol) gave **3** (459 mg, 88%) as an oil: IR (neat) 1700 cm^{-1}; ^1H NMR ($CDCl_3$ at 65 °C) δ 6.26 (td, 1 H, *J* = 10.3, 16.8 Hz, H4′), 6.02 (dd, 1 H, *J* = 15.0, 10.3 Hz, H3′), 5.66 (dt, 1 H, *J* = 15.0, 16.0 Hz, H2′), 5.06 (d, 1 H, *J* = 16.8 Hz, H5′c), 4.95 (d, 1 H, *J* = 10.3 Hz, H5′t), 3.68 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$ at 60 °C) δ 156.1 (s), 136.9 (s,d), 134.2 (s), 133.6 (d), 130.5 (d), 128.9 (d), 127.0 (d), 126.7 (d), 126.1 (d), 54.9 (d), 52.4 (q), 40.1 (t), 38.4 (t), 28.5 (t). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.77; H, 7.63.

(±)-*allo*-13,14-Didehydro-18-oxoberban [(±)-(8a*S,12a*S**,13a*S**)-5,6,8a,9,10,12a,13,13a-Octahydro-8*H*-dibenzo[*a,g*]quinolizin-8-one] (5).** The reaction of **1** (728 mg; 2.0 mmol) with **2** (268 mg; 2.0 mmol) and acryloyl chloride (0.20 mL; 2.4 mmol) gave (±)-**5** (430 mg, 83%) as an oil: IR (neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.76–5.90 (m, 1 H, —CH=), 5.65–5.75 (m, 1 H, —CH=), 4.80–4.92 (m, 1 H, H3), 4.73 (dd, 1 H, *J* = 4.3, 11.6 Hz, H1); ^{13}C NMR ($CDCl_3$) δ 172.4 (s), 137.0 (s), 134.9 (s), 128.8 (d), 128.4 (d), 128.2 (d), 126.6 (d), 126.5 (d), 125.0 (d), 56.5 (d), 40.6 (d), 39.6 (t), 34.3 (t), 32.0 (d), 29.0 (t), 25.3 (t), 23.0 (t). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56. Found: C, 80.34, H, 7.51.

(±)-*allo*-7,8-Dimethoxy-13,14-didehydro-18-oxoberban [(±)-(8a*S,12a*S**,13a*S**)-5,6,8a,9,10,12a,13,13a-Octahydro-2,3-dimethoxy-8*H*-dibenzo[*a,g*]quinolizin-8-one] (7).** The reaction of **1** (826 mg; 2.3 mmol) with **6** (433 mg; 2.3 mmol) and acryloyl chloride (0.23 mL; 2.8 mmol) gave (±)-**7** (577 mg, 81%) as a semisolid: IR (neat) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.73 (s, 1 H), 6.65 (s, 1 H), 5.78–5.90 (m, 1 H, —CH=), 5.65–5.77 (m, 1 H, —CH=) 4.83–4.97 (m, 1 H, H3), 4.66 (dd, 1 H, *J* = 4.3, 11.6 Hz, H1) 3.89 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 172.2 (s), 147.8 (2s), 128.9 (s), 128.5 (d), 128.1 (d), 127.1 (s), 111.6 (d), 108.4 (d), 56.3 (d), 56.1 (q), 55.9 (q), 40.6 (t), 39.6 (d), 34.6 (t), 31.9 (d), 28.5 (t), 25.3 (t), 23.0 (t). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40. Found: C, 72.52; H, 7.36.

(±)-*allo*-7,8-Dimethoxyberban (8). Catalytic hydrogenation of (±)-**5** (200 mg; 0.64 mmol) with PtO_2 (20 mg) in MeOH (20 mL) gave (±)-7,8-dimethoxyberban-18-one (195 mg, 98%), which was reduced with $LiAlH_4$ (200 mg) in THF (8 mL) and ether (8 mL) to afford (±)-**8** (148 mg, 82%): mp 134–135 °C (lit.[21b] mp 133–134 °C); IR (Nujol) 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.72 (s, 1 H), 6.58 (s, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 2.71 (dd, 1 H, *J* = 2.0, 11.2 Hz), 2.56 (dd, 1 H, *J* = 3.4, 15.8 Hz); ^{13}C NMR ($CDCl_3$) δ 147.2 (s), 147.1 (s), 130.9 (s), 127.1 (s), 111.6 (d), 108.3 (d), 63.6 (d), 63.0 (t), 56.0 (q), 55.8 (q), 52.9 (t), 36.4 (d), 35.3 (d), 32.2 (t), 31.8 (t), 29.4 (t), 26.7 (t), 26.4 (t), 20.8 (t).

(±)-*allo*-4-Cyano-3,4,13,14-tetradehydro-18-oxoberban [(±)-(8a*S,12a*S**,13a*S**)-8a,9,10,12a,13,13a-Hexahydro-5-cyano-8*H*-dibenzo[*a,g*]quinolizin-8-one] (10a).** The reaction of **1** (365 mg; 1.0 mmol) with **9a** (158 mg; 1.0 mmol) and acryloyl chloride (0.10 mL; 1.2 mmol) gave (±)-**10a** (225 mg, 81%): mp 170–173 °C; IR (Nujol) 2214, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (s, 1 H, H3), 5.85–5.98 (m, 1 H, —CH=), 5.68–5.83 (m, 1 H, —CH=), 4.93 (dd, 1 H, *J* = 4.1, 11.5 Hz, H1); ^{13}C NMR ($CDCl_3$) δ 171.5 (s), 136.7 (s), 130.7 (s), 129.1 (d), 128.6 (d), 128.3 (d), 127.9 (d), 126.7 (s), 123.9 (d), 123.2 (d), 116.6 (s), 95.9 (s), 55.9 (s), 40.5 (d), 31.1 (d), 30.5 (t), 24.8 (t), 23.0 (t). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84. Found: C, 77.96; H, 5.85.

(±)-*allo*-4-Formyl-3,4,13,14-tetradehydro-18-oxoberban [(±)-(8a*S,12a*S**,13a*S**)-8a,9,10,12a,13,13a-Hexahydro-5-formyl-8*H*-dibenzo[*a,g*]quinolizin-8-one] (10b).** The reaction of **1** (358 mg; 1.0 mmol) with **9b** (159 mg; 1.0 mmol) and acryloyl chloride (0.10 mL; 1.2 mmol) gave (±)-**10b** (184 mg, 66%): mp 148–149 °C; IR (Nujol) 1685, 1665 cm^{-1}, ^1H NMR ($CDCl_3$) δ 9.65 (s, 1 H, CHO), 8.11 (s, 1 H, H3), 5.83–5.98 (m, 1 H, —CH=), 5.66–5.80 (m, 1 H, —CH=), 4.89 (dd, 1 H, *J* = 4.1, 11.3 Hz, H1); ^{13}C NMR ($CDCl_3$) δ 189.9 (d), 172.3 (s), 144.7 (d), 131.6 (s), 128.4 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.4 (s), 124.9 (d), 123.5 (d), 120.2 (s), 56.3 (d), 40.6 (d), 31.1 (t and d), 24.7 (t), 23.0 (t); HRMS calcd for $C_{18}H_{17}NO_2$ 279.1260, found 279.1259.

(±)-*allo*-4-(Methoxycarbonyl)-3,4,13,14-tetradehydro-18-oxoberban [(±)-(8a*S,12a*S**,13a*S**)-8a,9,10,12a,13,13a-Hexahydro-5-(methoxycarbonyl)-8*H*-dibenzo[*a,g*]quinolizin-8-one] (10c).** The reaction of **1** (386 mg; 1.1 mmol) with **9c** (192 mg; 1.0 mmol) and acryloyl chloride (0.10 mL; 1.2 mmol) gave (±)-**10c** (198 mg, 64%): mp 142–148 °C; IR (Nujol) 1710, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43 (s, 1 H, H3), 5.83–5.95 (m, 1 H, —CH=), 5.61–5.83 (m, 1 H, —CH=), 4.73 (dd, 1 H, *J* = 4.1, 11.7 Hz, H1), 3.88 (s, 3 H, OCH_3): ^{13}C NMR ($CDCl_3$) δ 172.1 (s), 166.0 (s), 135.8 (d), 132.2 (s), 129.0 (s), 128.2 (d), 128.1 (d), 127.9 (d), 127.6 (d), 124.9 (d), 123.1 (d), 112.5 (s), 55.9 (d), 51.5 (q), 40.7 (d), 31.2 (d) 30.1 (t), 25.1 (t), 23.0 (t); HRMS calcd for $C_{19}H_{19}NO_3$ 309.1366, found 309.1364.

Reaction of 2,4-Pentadienyltributyltin (1, *E*/*Z* = 25/75) with 2 Activated by Methyl Chloroformate. The reaction of **1** (*E*/*Z* = 25/75, 369 mg; 1.0 mmol), prepared from tributyltin chloride and pentadienyl anion generated by treatment of 1,4-pentadiene with *t*-BuOK–*n*-BuLi, with **2** (130 mg; 1.0 mmol) and $ClCO_2Me$ (0.10 mL; 1.2 mmol) gave **3** (201 mg, 79%).

(37) It has been reported that the intramolecular photocyclization of 2-[2′-[(trimethylsilyl)methyl]benzyl]-3-[(*tert*-butyldimethylsiloxy)methyl]-3,4-dihydroisoquinolinium salt gives an anticyclization product predominantly (up to 42% de).[36c]

(38) Pelletier, J. C.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 616.

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Reaction of 2,4-Pentadienyltributyltin (1, *E*/*Z* = 25/75) with 2 Activated by Acryloyl Chloride. The reaction of 1 (*E*/*Z* = 25/75, 403 mg; 1.1 mmol) with 2 (143 mg; 1.1 mmol) and acryloyl chloride (0.10 mL; 1.2 mmol) gave (±)-5 (214 mg, 77%).

(±)-*allo*-16,17-Didehydro-21-oxoyohimban [(±)-(4a*S,13b*S**,14a*S**)-3,4,4a,5,7,8,13,13b,14,14a-Decahydrobenz[*g*]indolo[2,3-*a*]quinolizin-5-one] (12).** The reaction of 1 (366 mg; 1.0 mmol) with 11 (176 mg; 1.0 mmol) and acryloyl chloride (0.10 mL; 1.2 mmol) was conducted under ice-cooling for 2 h. Then C_6H_6 (50 mL) was added to the reaction mixture, and the mixture was heated at reflux for 3 h. Chromatography on silica gel afforded (±)-12 (223 mg, 74%): mp 248–251 °C dec; IR (Nujol) 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (br s, 1 H, NH), 7.58 (d, 1 H, *J* = 8.0 Hz), 5.80–5.95 (m, 1 H, —CH═), 5.65–5.78 (m, 1 H, —CH═), 5.13–5.35 (m, 1 H, H3), 4.85 (dd, 1 H, *J* = 4.2, 11.2 Hz, H1); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 173.8 (s), 137.1 (s), 133.8 (s), 128.6 (d), 128.4 (d), 127.0 (s), 122.0 (d), 119.5 (d), 118.3 (d), 111.5 (d), 108.5 (s), 54.9 (d), 41.5 (d), 40.8 (t) 32.7 (t), 32.0 (d), 25.7 (t), 23.4 (t), 21.4 (t). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89. Found: C, 78.09; H, 6.88.

(±)-*allo*-Yohimban (13). Catalytic hydrogenation of (±)-12 (245 mg; 0.85 mmol) with 5% Pd–C (490 mg) in MeOH (40 mL) gave (±)-yohimban-21-one (206 mg, 83%), a portion of which (149 mg; 0.51 mmol) was reduced with $LiAlH_4$ (196 mg; 5.2 mmol) in THF (16 mL) to afford (±)-13 (127 mg, 91%): mp 153–155 °C (lit.[24b] mp 146–147 °C); ^1H NMR ($CDCl_3$) δ 7.79 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 136.2 (s), 135.9 (s), 127.5 (s), 121.1 (d), 119.3 (d), 118.0 (d), 110.7 (d), 108.1 (s), 62.0 (t), 60.6 (d), 53.5 (t), 36.7 (d), 34.8 (d), 31.6 (t), 30.4 (t), 26.6 (t), 26.5 (t), 21.8 (t), 20.9 (t).

Preparation of 2-Vinyl-3-butenol (16). To a suspension of vinylmagnesium bromide (120 mmol) in ether (130 mL) was added butadiene monoepoxide (2.80 g; 40 mmol) in ether (20 mL), and the reaction mixture was heated at reflux for 3 h. To the ice-cooled reaction mixture was carefully added 10% aqueous NH_4Cl (15 mL). The organic layer was washed with water and brine and dried ($MgSO_4$). The solvent was carefully evaporated, and the residue was distilled under reduced pressure with a trap cooled by liquid N_2 to afford 16 (2.04 g, 52%) containing a small amount of 17 (94:6 by GLC analysis). 16: ^1H NMR ($CDCl_3$) δ 3.57 (t, 2 H, *J* = 6.3 Hz), 2.94–3.00 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 137.3 (d), 117.0 (t), 65.0 (t), 50.7 (d).

[3-(Hydroxymethyl)-2,4-pentadienyl]trimethyltin (19). Two typical procedures that selectively produce either (*Z*)- or (*E*)-19 are described here. Method A: To a solution of *n*-BuLi (hexane, 1.66 M, 1.57 mL; 2.5 mmol) and TMEDA (0.38 mL) in ether (5 mL) below −70 °C was added 16 (105 mg, 1.1 mmol) in ether (1 mL). After DME (2 mL) was added to this solution, the temperature was gradually raised to 0 °C for 1.5 h, and the mixture was stirred under ice-cooling for 3 h. The reaction mixture was cooled to below −70 °C, and the solution of Me_3SnCl (400 mg, 2.0 mmol) in ether (2 mL) was added. The temperature was gradually raised to 0 °C over a period of 1.5 h, and the reaction mixture was stirred under ice-cooling for 0.5 h. The mixture was kept below −20 °C while ether (30 mL) and then 10% aqueous NH_4Cl (10 mL) were added. The organic layer was washed with water and brine and dried ($MgSO_4$). The solvent was evaporated, and the residue was quickly chromatographed on silica gel to afford 19 (133 mg, 48%), which was labile at rt in the condensed state. The *Z*/*E* ratio was determined to be 96:4 by ^1H NMR. (*Z*)-19: ^1H NMR ($CDCl_3$) δ 6.25 (dd, 1 H, *J* = 10.9 and 17.4 Hz, H4), 5.85 (t, 1 H, *J* = 9.6 Hz, H2), 5.15 (d, 1 H, *J* = 17.4 Hz, H5c), 4.86 (d, 1 H, *J* = 10.9 Hz, H5t), 4.30 (d, 2 H, *J* = 5.7 Hz, CH_2OH), 1.94 (dt, 2 H, *J* = 9.6 and 35.1 Hz, H1), 1.29 (t, 1 H, *J* = 5.7 Hz, OH), 0.11 (t, 9 H, *J* = 26.2 Hz, $3CH_3$); ^{13}C NMR ($CDCl_3$) δ 139.0 (d), 136.3 (d), 132.4 (s), 108.8 (t), 56.4 (t), 14.5 (t), −9.5 (q); ^{119}Sn NMR ($CDCl_3$, TMT) δ 3.9. Method B: To a solution of *n*-BuLi (1.66 M in hexane, 1.57 mL, 2.5 mmol) and TMEDA (0.38 mL) in DME (5 mL) kept below −70 °C was added 16 (101 mg, 1.0 mmol) in DME (1 mL). The temperature was gradually raised to 0 °C over a period of 1.5 h, and the mixture was stirred under ice-cooling for 2.5 h. To the ice-cooled reaction mixture was added a solution of Me_3SnCl (236 mg, 1.2 mmol) in DME (1 mL), and the mixture was stirred for 0.5 h. A workup similar to the one above gave 19 (132 mg, 49%). The *Z*/*E* ratio was determined to be 30:70 by ^1H NMR. NMR spectral data of (*E*)-19 was elucidated from the NMR of the mixture of the stereoisomers. (*E*)-19: ^1H NMR ($CDCl_3$) δ 6.56 (dd, 1 H, *J* = 17.7 and 11.2 Hz, H4), 5.85 (t, 1 H, *J* = 10.2 Hz, H2), 5.28 (d, 1 H, *J* = 17.7 Hz, H5c), 5.06 (d, *J* = 11.2 Hz, H5t), 4.23 (d, 2 H, *J* = 5.9 Hz, CH_2OH), 1.89 (H1, dt, 2 H, *J* = 10.2 and 35.1 Hz, H1), 1.40 (t, 1 H, *J* = 5.6 Hz, OH), 0.10 (t, 9 H, *J* = 26.3 Hz, $3CH_3$); ^{13}C NMR ($CDCl_3$) δ 132.6 (d), 131.1 (d, s), 112.2 (t), 65.0 (t), 13.4 (t), −9.5 (q); ^{119}Sn NMR ($CDCl_3$, TMT) δ 8.6.

The stereochemistries of (*Z*)- and (*E*)-19 were determined from difference ^1H NMR NOE spectra: irradiation of H1 enhanced the signal due to H6 in (*Z*)-19, and irradiation of H1 in (*E*)-19 enhanced the one due to H4.

(±)-*allo*-16-(Hydroxymethyl)-16,17-didehydro-21-oxoyohimban [(±)-(4a*S,13b*S**,14a*S**)-3,4,4a,5,7,8,13,13b,14,14a-decahydro-1-(hydroxymethyl)benz[*g*]indolo[2,3-*a*]quinolizin-5-one] (20).** The reaction of 11 (80 mg; 0.47 mmol) with 19 (130 mg; 0.50 mmol) and acryloyl chloride (0.04 mL; 0.50 mmol) was conducted under ice-cooling for 2 h. Then C_6H_6 (30 mL) was added to the reaction mixture, and the mixture was heated at reflux for 3 h. Chromatography on silica gel gave (±)-20 (96 mg, 63%): mp 158–160 °C; IR (Nujol) 3300, 1728, 1602, 1283 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (br s, 1 H, NH), 7.51 (d, 1 H, *J* = 8.1 Hz), 7.33 (d, 1 H, *J* = 8.0 Hz), 5.84 (br s, 1 H, —CH═), 5.18 (m, 1 H, H3), 4.81 (br d, 1 H, *J* = 7.3 Hz, H1), 4.25 (d, 1 H, *J* = 9.0 Hz), 4.14 (d, 1 H, *J* = 9.0 Hz); ^{13}C NMR (CD_3OD) δ 174.6 (s), 138.9 (s), 137.8 (s), 134.4 (s), 127.5 (s), 125.5 (d), 122.3 (d), 119.8 (d), 118.7 (d), 111.9 (d), 108.5 (s), 65.1 (t), 55.6 (d), 42.5 (d), 41.3 (t), 32.3 (d), 31.6 (t), 25.9 (t), 23.9 (t), 21.8 (t); HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1683, found 322.1670.

(±)-Nitraraine (21). Treatment of (±)-20 (90 mg; 0.28 mmol) with *t*-$BuMe_2SiCl$ (50 mg; 0.33 mmol) and imidazole (50 mg, 0.76 mmol) in DMF (3 mL) and subsequent reduction with $LiAlH_4$ (100 mg; 2.6 mmol) in THF (5 mL) and deprotection with Bu_4NF (THF, 1.0 M, 0.60 mL; 0.6 mmol) in THF (5 mL) afforded (±)-21 (49 mg, 57%): mp 122–124 °C (lit.[26] mp 114–116 °C); ^1H NMR ($CDCl_3$) δ 8.00 (br s, 1 H), 7.44 (d, 1 H, *J* = 7.3 Hz), 7.29 (d, 1 H, *J* = 7.9 Hz), 7.05–7.14 (m, 2 H), 5.68 (br s, 1 H), 4.18 (d, 1 H, *J* = 12.5 Hz), 4.05 (d, 1 H, *J* = 12.5 Hz), 3.09 (d, 1 H, *J* = 11.6 Hz); ^{13}C NMR ($CDCl_3$) δ 140.5 (s), 136.1 (s), 135.5 (s), 127.4 (s), 125.0 (d), 121.1 (d), 119.2 (d), 118.0 (d), 110.9 (d), 108.0 (s), 65.9 (t), 61.5 (t), 60.3 (d), 53.6 (t), 35.7 (d), 34.5 (d), 32.3 (t), 25.8 (t), 23.4 (t), 21.7 (t).

The ^1H NMR spectrum (400 MHz) of (±)-21 is essentially identical to that (500 MHz) of (−)-21.

(*S*)-3-(Hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline (24). Ethyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (23) was prepared from L-phenylalanine (22) by the reported procedures for the synthesis of (±)-23.[36a] Reduction of (*S*)-23 (29.3 g, 143 mmol) with $LiAlH_4$ (27.7 g) in ether (700 mL) gave (*S*)-24 (16.5 g, 71%) as colorless crystals: mp 119–120 °C; $[\alpha]^{24}_D$ = −92.8° (*c* = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.04 (s, 2 H), 3.75 (dd, 1 H, *J* = 3.6 and 10.9 Hz), 3.50 (dd, 1 H, *J* = 7.9 and 10.9 Hz), 2.99–3.09 (m, 1 H), 2.84 (br s, 2 H), 2.71 (dd, 1 H, *J* = 4.4 and 16.2 Hz), 2.56 (dd, 1 H, *J* = 10.6 and 16.3 Hz); ^{13}C NMR ($CDCl_3$) δ 135.4 (s), 134.1 (s), 129.3 (d), 126.1 (d), 126.0 (d), 125.9 (s), 65.5 (t), 55.2 (d), 47.9 (t), 31.0 (t). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.86, H, 8.07. The enantiomeric excess was determined to be 98% by HPLC analysis (Daisel Chiracel OD, hexane/*i*-PrOH = 97/3, 1.0 mL/min, 254 nm).

(*S*)-3-[(Trimethylsiloxy)methyl]-3,4-dihydroisoquinoline (25). Treatment of (*S*)-24 (1.00 g, 6.1 mmol) with Me_3SiCl (0.93 mL, 7.3 mmol) and Et_3N (1.02 mL, 7.3 mmol) in THF (13 mL) gave the trimethylsiloxy derivative of (*S*)-24 (1.43 g, 100%). The trimethylsiloxy derivative (1.40 g) was dissolved in CH_2Cl_2 (10 mL), and to the CH_2Cl_2 solution was added NCS (1.17 g; 8.8 mmol). After 1 h, Bu_4NI (219 mg; 0.6 mmol) and 20% aqueous KOH (9 mL) were added to the mixture. The reaction mixture was stirred for 1 h, and the organic layer was washed with water and dried (Na_2SO_4). The solvent was evaporated to give (*S*)-3-(hydroxymethyl)-3,4-dihydroisoquinoline (851 mg, 89%). Treatment of this imino alcohol (810 mg, 5.0 mmol) with Me_3SiCl (0.764 mL, 6.02 mmol) and Et_3N (0.840 mL, 6.0 mmol) in THF (10 mL) afforded (*S*)-25 (811 mg, 69%): bp 92 °C/0.19 mm; $[\alpha]^{25}_D$ +61.3° (*c* = 1.00, C_2H_5OH); IR (neat) 1625, 1105, 1079 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.32 (d, 1 H, *J* = 2.0 Hz), 2.86 (dd, 1 H, *J* = 5.5 and 16.4 Hz) 2.65 (dd, 1 H, *J* = 10.4 and 16.4 Hz), 0.09 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 160.4 (d), 136.0 (s), 131.1 (d), 128.5 (s), 127.8

(d), 127.2 (d), 127.0 (d), 66.0 (t), 58.7 (d), 27.6 (t), -0.54 (q). Anal. Calcd for $C_{13}H_{19}NOSi$: C, 66.90; H, 8.21. Found: C, 66.78; H, 8.14.

Three-Component Coupling Reaction of 1 with (*S*)-25 and Acryloyl Chloride. The reaction of 1 (364 mg; 1.0 mmol) with (*S*)-**25** (241 mg; 1.0 mmol) and acryloyl chloride (0.10 mL; 1.2 mmol) under ice-cooling for 2 h and then at rt (15–20 °C) for 21 h gave (1*R*,3*S*,12*R*,17*R*)-3-(hydroxymethyl)-13,14-didehydro-18-oxoberban [(6*S*,8a*R*,12a*R*,13a*R*)-5,6,8a,9,10,12a,13,13a-octahydro-6-(hydroxymethyl)-8*H*-dibenzo[*a*,*g*]quinolizin-8-one] (**26a**) (167 mg), (1*S*,3*S*,12*S*,17*S*)-3-(hydroxymethyl)-13,14-didehydro-18-oxoberbane [(6*S*,8a*S*,12a*S*,13a*S*)-5,6,8a,9,10,12a,13,13a-octahydro-6-(hydroxymethyl)-8*H*-dibenzo[*a*,*g*]quinolizin-8-one] (**26b**) (23 mg), and a mixture of **26a** and **26b** (32 mg, **26a**:**26b** = 72:28 by HPLC analysis). The total yield was 222 mg (79%), and the diastereomeric excess was 76%. **26a**:[43] mp 150–151 °C; $[\alpha]^{27}_D$ +235° (*c* = 1.00, C_2H_5OH); IR (Nujol) 3378, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.77–5.80 (m, 1 H, —CH=), 5.63–5.67 (m, 1 H, —CH=), 5.28–5.36 (m, 1 H, H3), 4.69 (dd, 1 H, *J* = 3.6 and 11.5 Hz, H1), 3.48–3.65 (m, 2 H, CH_2OH), 3.05 (dd, 1 H, *J* = 5.9 and 16.5 Hz), 2.47 (d, 1 H, *J* = 13.5 Hz); ^{13}C NMR ($CDCl_3$) δ 174.4 (s), 135.6 (s), 131.9 (s), 129.4 (d), 128.4 (d), 128.1 (d), 126.8 (d), 126.4 (d), 125.1 (d), 61.8 (t), 53.3 (d), 48.4 (d), 47.7 (d), 40.8 (d), 35.0 (t), 32.0 (d), 29.5 (t), 25.1 (t), 23.2 (t). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47. Found: C, 76.35; H, 7.57. **26b**: mp 150 °C dec; ^1H NMR ($CDCl_3$) δ 5.75–5.79 (m, 1 H, —CH=), 5.62–6.65 (m, 1 H, H1, —CH=), 4.71–4.78 (m, 1 H, H3), 4.66 (t, 1 H, *J* = 5.7 Hz, H1), 3.03 (dd, 1 H, *J* = 6.3 and 15.5 Hz), 2.73 (dd, 1 H, *J* = 6.9 and 15.8 Hz); ^{13}C NMR ($CDCl_3$) δ 175.3 (s), 136.9 (s), 133.8 (s), 129.4 (d), 128.6 (d), 128.3 (d), 127.4 (d), 126.8 (d), 123.6 (d), 65.7 (t), 51.7 (d), 51.6 (d), 43.3 (d), 34.0 (t), 33.0 (d), 30.1 (t), 25.7 (t), 22.6 (t); HRMS calcd for $C_{18}H_{21}NO_2$ 283.1573, found 283.1567.

(*S*)-3-[(*tert*-Butyldimethylsiloxy)methyl]-3,4-dihydroisoquinoline (27). Treatment of (*S*)-**24** (1.00 g, 6.1 mmol) with *t*-$BuMe_2SiCl$ (1.02 g; 6.7 mmol) and imidazole (835 mg, 12.3 mmol) in DMF (6 mL) gave the *tert*-butyldimethylsiloxy derivative of (*S*)-**24** (1.69 g, 99%). The *tert*-butyldimethylsiloxy derivative (1.69 g, 6.1 mmol) was dissolved in CH_2Cl_2 (10 mL), and to the CH_2Cl_2 solution was added NCS (1.20 g; 9.0 mmol). After 1 h, Bu_4NI (249 mg; 0.67 mmol) and 30% aqueous KOH (15 mL) were added to the mixture. The reaction mixture was stirred for 1 h, and the organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent followed by distillation gave (*S*)-**27** (1.47 g, 87%): bp 97–99 °C/0.13 mm; $[\alpha]^{30}_D$ +81.2° (*c* = 1.00, C_2H_5OH); IR (neat) 1627, 1106, 1084 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.33 (d, 1 H, *J* = 2.0 Hz), 2.91 (dd, 1 H, *J* = 5.6 and 16.2 Hz), 2.69 (dd, 1 H, *J* = 10.9 and 16.2 Hz), 0.91 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 160.4 (d), 136.0 (s), 131.2 (d), 128.6 (s), 127.2 (d), 126.9 (d), 66.5 (t), 58.9 (d), 27.7 (t), 25.9 (q), 18.3 (s), -5.4 (q). Anal. Calcd for $C_{16}H_{25}NOSi$: C, 69.76; H, 9.15. Found: C, 69.80; H, 9.44.

Three-Component Coupling Reaction of 1 with (*S*)-27 and Acryloyl Chloride. The reaction of 1 (358 mg, 1.0 mmol) with (*S*)-**27** (276 mg, 1.0 mmol) and acryloyl chloride (0.10 mL, 1.2 mmol) under ice-cooling for 2 h and then rt (15–20 °C) for 46 afforded (1*R*,3*S*,12*R*,17*R*)-3-[(*tert*-butyldimethylsiloxy)methyl]-13,14-didehydro-18-oxoberban [(6*S*,8a*R*,12a*R*,13a*R*)-5,6,8a,9,10,-12a,13,13a-octahydro-6-[(*tert*-butyldimethylsiloxy)methyl]-8*H*-dibenzo[*a*,*g*]quinolizin-8-one] (**28**) (325 mg, 82%): ^1H NMR ($CDCl_3$) δ 5.78–5.83 (m, 1 H, —CH=), 5.63–5.68 (m, 1 H, —CH=), 5.22–5.27 (m, 1 H, H3), 4.62 (dd, 1 H, *J* = 3.6 and 11.3 Hz, H1), 3.56 (d, 2 H, *J* = 7.2 Hz, CH_2OSi), 3.00 (dd, 1 H, *J* = 6.0 and 16.5 Hz), 2.80 (dd, 1 H, *J* = 2.0 and 16.5 Hz), 0.82 (s, 9 H, $3CH_3$), -0.04 (s, 6 H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ 173.1 (s), 136.2 (s), 132.5 (s), 129.5 (d), 128.6 (d), 128.2 (d), 126.8 (d), 126.3 (d), 124.9 (d), 61.3 (t), 53.7 (d), 47.7 (d), 40.8 (d), 35.0 (t), 32.2 (d), 29.1 (t), 25.7 (q), 25.2 (t), 23.2 (t), 18.0 (s), -5.5 (q), -5.6 (q). To a solution of **28** (241 mg; 0.61 mmol) in THF (9 mL) was added Bu_4NF (THF, 1.0 M, 2.1 mL). The reaction mixture was stirred for 30 min, and water (20 mL) was added to it. The mixture was extracted with ether, and the organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was analyzed by HPLC (μBondasphere 5 μm Si-100Å, hexane:*i*-PrOH = 97:3, 1 mL/min, 254 nm). The diastereomeric excess was 94%. The residue was chromatographed on silica gel to afford **26a** (0.133 g, 77%). ^{19}F NMR analysis of the MTPA ester of **26a** showed that its enantiomeric excess was 94%.

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Supplementary Material Available: Full details of experiments and spectral data (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(43) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1ZE, UK.