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Development of Diastereoselective Birch Reduction−Alkylation Reactions of Bi- and Tricyclic β-Alkoxy-α,β-unsaturated Ketones

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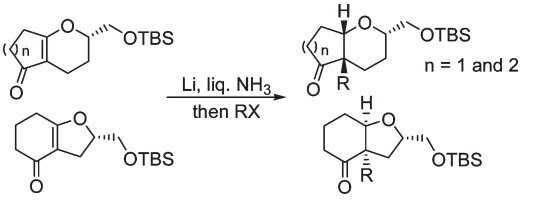

Diastereoselective Birch reduction−alkylation reactions of bicyclic β-alkoxy-α,β-unsaturated carbonyl compounds and tricyclic analogues were investigated. Although the relative configuration of the product was altered according to the structure of the starting material, stereoselectivity of the reaction could be accounted for by similar reaction pathways. The product from the tricyclic β-alkoxy-α,β-unsaturated carbonyl compound corresponded to the trichothecene skeleton.

Introduction

Chiral quaternary carbon centers at the angular position, which frequently occur in alkaloids or terpenoids, are generally difficult to construct with high optical purity.[1] Because such compounds are known to possess unique biological activities, there is currently a critical need in organic chemistry to develop a general and efficient method for preparing chiral quaternary carbon centers, especially at the angular position. The most famous procedure for preparing compounds having an asymmetric center at the angular position is a chiral amino acid catalyzed cyclization reaction of prochiral 1,3-cyclohexanedione derivatives to give a Wieland−Miescher-type ketone.[2,3] When the substituent group (R) is a methyl group, the bicyclic compound could be obtained with high optical purity.[2a,f,h,i] However, if the R is another group, a serious decrease in optical purity is observed, and sometimes a stoichiometric amount of proline must be used to complete the reaction.[2d,g]

In the course of our continuous investigation to establish a general method for constructing an asymmetric quaternary carbon center, we previously published the strong Brønsted acid promoted cyclization reaction of the acetal **1** to β-alkoxy-α,β-unsaturated ketone **2a**, followed by the introduction of an allyl group at the angular position in the corresponding TBS (tert-butyldimethylsilyl) ether **2b** by a diastereoselective Birch reduction−alkylation reaction.[4,5] Moreover, we succeeded in the synthesis of two diastereo-

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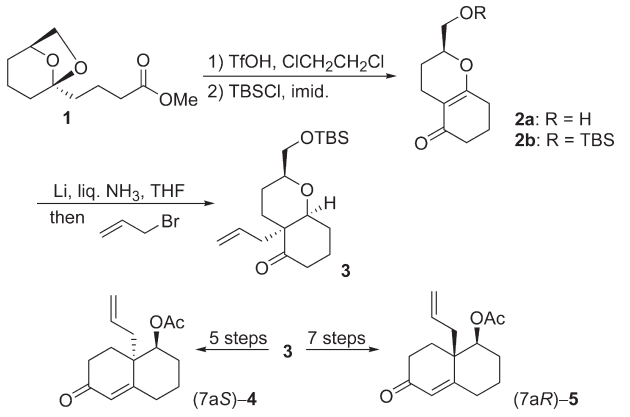
SCHEME 1. Diastereoselective Birch Reduction−Alkylation Reaction and Its Application

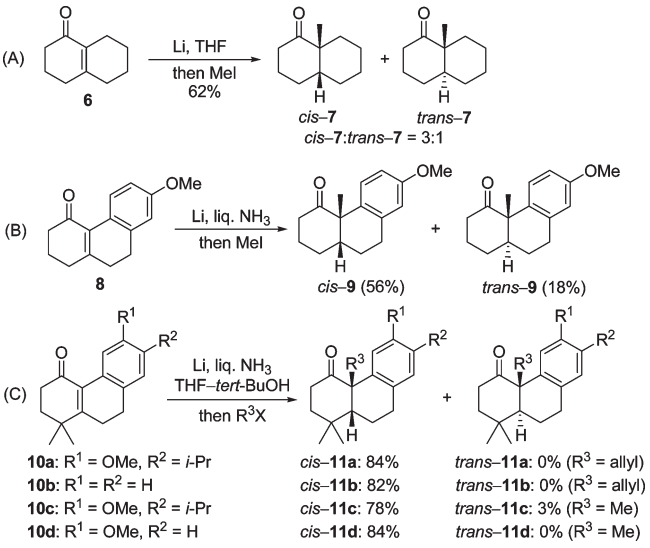


mers, (7a*S*)-**4** and (7a*R*)-**5**, whose absolute configurations at the angular position were opposite to each other, from **3** as a common intermediate (Scheme 1).[5]

The sequential Birch reduction−alkylation reaction was originally developed by Stork et al. in 1961,[6] and it has been applied to synthesize many natural products.[7] However, only two kinds of substrates can be found in the literature for the reduction−alkylation reaction of a *β*-alkoxy-α,*β*-unsaturated carbonyl compound. The first one is the reaction of *N*,*N*-dialkyl-3-furamide derivatives as substrates,[8] and the latter example is enantioselective reductive alkylation of chiral 2-alkoxybenzamide derivatives.[9] Both examples contain aromatic rings (furan and benzene), and applications of the reduction−alkylation reaction to *β*-alkoxy-α,*β*-unsaturated carbonyl compounds, which do not contain aromatic ring(s), have not been reported yet to the best of our knowledge.[10]

Stork et al. reported the isolation of two compounds, *cis*-**7** and *trans*-**7**, in an approximate 3:1 ratio by a Birch reduction−alkylation reaction of 3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (**6**)[11a] (Scheme 2A). An identical result

SCHEME 2. Previous Examples of Birch Reduction−Alkylation Reactions



using tricyclic substrate **8** was reported by Mukherjee in 1984[11b] (Scheme 2B), and an exclusively cis-controlled reaction of **10** was performed at a later time[11c−f,12] (Scheme 2C).

In the case of our substrate shown in Scheme 1, not only did we observe a cis configuration between cyclohexanone and tetrahydropyran rings, but we also observed high diastereoselectivity between the side chain (−CH_2OTBS) and the incorporated allyl group. This result prompted us to investigate the generality of this reaction for different kinds of substrates. In this article, we report the full details of the reduction−alkylation reaction and the results of reactions of compounds having different ring sizes, **2b**, **12b**, and **13b** and more rigid structure **14**, which correspond to the synthesis of the trichothecene skeleton (Figure 1).

Results and Discussion

1. Synthesis of the Starting Materials. We planned the synthesis of bicyclic *β*-alkoxy-α,*β*-unsaturated ketone derivatives **12b** from 1,3-cyclopentanedione (**17**) with **19** and **13b** from 1,3-cyclohexanedione (**18**) with **20** via 2-alkyl-1,3-cycloalkanediones **15** and **16**, respectively (Figure 2). It is well-known that the Knoevenagel reaction between **18** and an aldehyde gives the dimerized compound **21** as a major product. The difficulty in forming **22** was reported as well.[2d,13] Therefore, we focused on the ingenious Knoevenagel hydrogenation reaction published by Ramachary and Kishor to synthesize **15** and **16**, respectively.[2d,14]

The aldehyde **19**[15] was subjected to the Knoevenagel hydrogenation reaction with 1,3-cyclopentanedione (**17**) in the presence of dihydropyridine **23**, and a catalytic amount of L-proline[2d] gave an almost quantitative yield of 2-substituted

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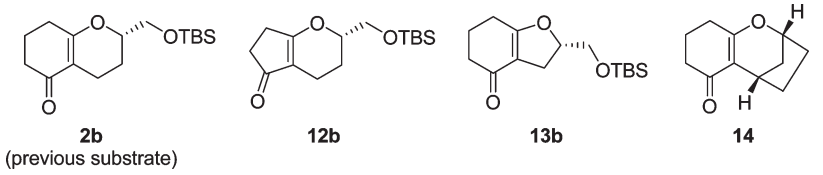


FIGURE 1. Bi- and tricyclic β-alkoxy-α,β-unsaturated carbonyl compounds.

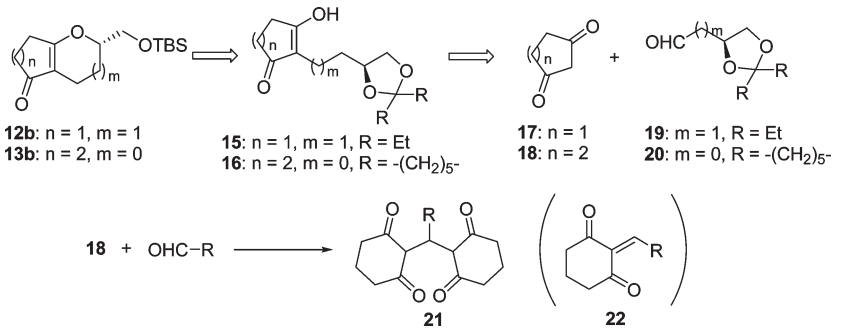
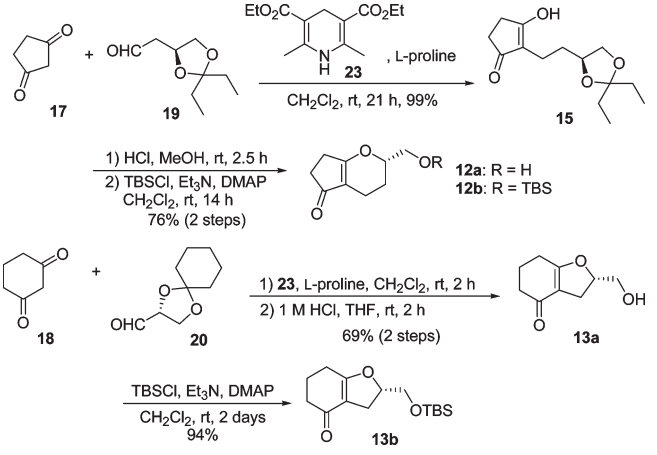


FIGURE 2. Retrosynthetic analysis of **12b** and **13b**.

SCHEME 3. Synthesis of 12b and 13b



ketone **15**. The acetal of **15** was hydrolyzed by treatment with HCl in methanol,[16] and the desired product **12b** was formed with a yield of 76% by protection of the primary alcohol by the TBS group. In almost the same procedure, **13b** was synthesized from 1,3-cyclohexanedione (**18**) and the aldehyde **20**[17] via **13a** with good overall yield (Scheme 3).

2. Stereoselective Birch Reduction−Alkylation Reaction. The results of a Birch reduction−alkylation reaction with three different substrates are summarized in Table 1. In most cases, the addition of isoprene to oxidize the excess amount of lithium was effective in obtaining the product in good yield [e.g., entry 1 (36%) vs 3 (61%) and entry 2 (45%) vs 4 (70%)]. The alkylated compounds **24a**, **24b**, and **24c** were isolated from **2b** by treatment with allyl bromide [entries 1 (36%) and 3 (61%)], methyl iodide [entries 2 (45%) and 4 (70%)], and benzyl bromide [entry 5 (53%)] as the sole products, respectively. Unfortunately, it was also noted that the reduction−alkylation reaction of **2b** has serious limitations. Namely, both ethyl iodide and 2-iodopropane did not react at all with the enolate derived from **2b**, and only protonated compounds (two diastereomers) were observed together with inseparable decomposed compounds in quite low yield (entries 6 and 7). Furthermore, desired alkylated compounds **24f**, **24g**, and **24h** could not be obtained in the reactions with the reagents having high reactivity (BOMCl, MOMCl, and $TMSCH_2Cl$), while compound **24i**, whose stereochemistry between angular positions is cis, was isolated in good yield [entries 8 (67%), 9 (70%), and 10 (74%)]. Although the exact reason for the protonation has not been clear yet, one possible way might be considered as follows: the halide reacted with ammonia much faster than with the enolate, followed by protonation of the enolate, which was proceeded by the resulting ammonium cation. From the results shown above, we concluded that the halides, which can be used for the reduction−alkylation reaction of bicyclic β-alkoxy-α,β-unsaturated ketone derivatives, have to satisfy the following requirements: (1) they must not have a sp^3 β-carbon with hydrogen, and (2) they must have enough reactivity but must not be activated so as to react with ammonia.

Although the alkyl halides are limited, the alkylated compounds **25a**, **25b**, **26a**, and **26b** were isolated as single compounds by treatment with allyl bromide [entries 11 (58%) and 13 (52%)] or methyl iodide [entries 12 (68%) and 14 (25%)] with **12b** or **13b**, respectively, and reasonable yields were observed with the recovery of the starting materials in some cases (entries 11, 12, and 14).

The determination of the configuration of **24a** was described in our previous paper.[5] The structures of **24b**, **24c**, **25b**, and **26b** were estimated by analogy to the ^1H and ^{13}C NMR spectra of **24a**, **25a**, and **26a**, respectively. The stereochemistries of **24i**, **25a**, and **26a** were determined by careful analysis of their ^1H NMR spectra and NOESY experiments, which are shown in Figure 3.

$H^{4\alpha}$ and $H^{4\beta}$ in **24i** were distinguishable because the chemical shift of $H^{4\alpha}$ was observed at low field (2.35−2.44 ppm), which was caused by the deshielding effect of

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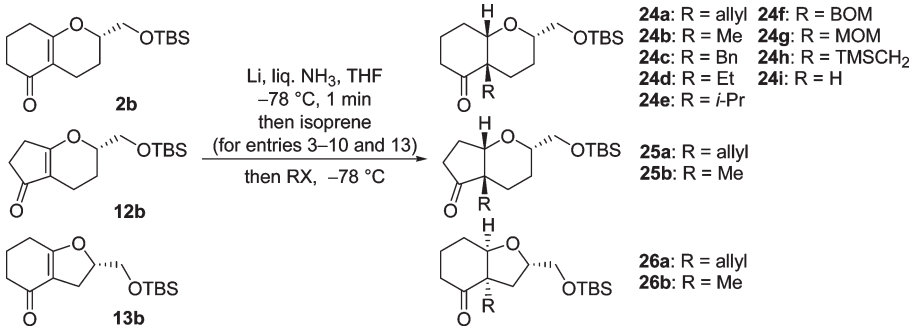
TABLE 1. Diastereoselective Birch Reduction−Alkylation Reactions of 2b, 12b, and 13b[a]



entry	substrate	RX	time	isoprene	product	yield of the product (%)	recovery of the starting material (%)
1[b]	**2b**	allyl bromide	50 min	−	**24a**	36	0
2		methyl iodide	50 min	−	**24b**	45	0
3		allyl bromide	1.5 h	+	**24a**	61	0
4		methyl iodide	40 min	+	**24b**	70	0
5		benzyl bromide	1 h	+	**24c**	53	0
6		ethyl iodide	1.5 h	+	**24d**	0	0
7		2-iodopropane	1.5 h	+	**24e**	0	0
8		BOMCl[d]	1 h	+	**24i**	67	0
9		MOMCl	1.5 h	+	**24i**	70	0
10		$TMSCH_2Cl$	1.25 h	+	**24i**	74	0
11	**12b**	allyl bromide	1.5 h	−	**25a**	58 (62)[c]	6
12		methyl iodide	1.5 h	−	**25b**	68 (73)[c]	7
13	**13b**	allyl bromide	1.5 h	+	**26a**	52	0
14		methyl iodide	1.5 h	−	**26b**	25 (38)[c]	35

[a]All products shown in the above figure were isolated as a single diastereomer. [b]The yield of **24a** is from ref 5. [c]The numbers in parentheses are the yields of the product based on the consumed starting material **12b** or **13b**. [d]BOM is (benzyloxy)methyl.

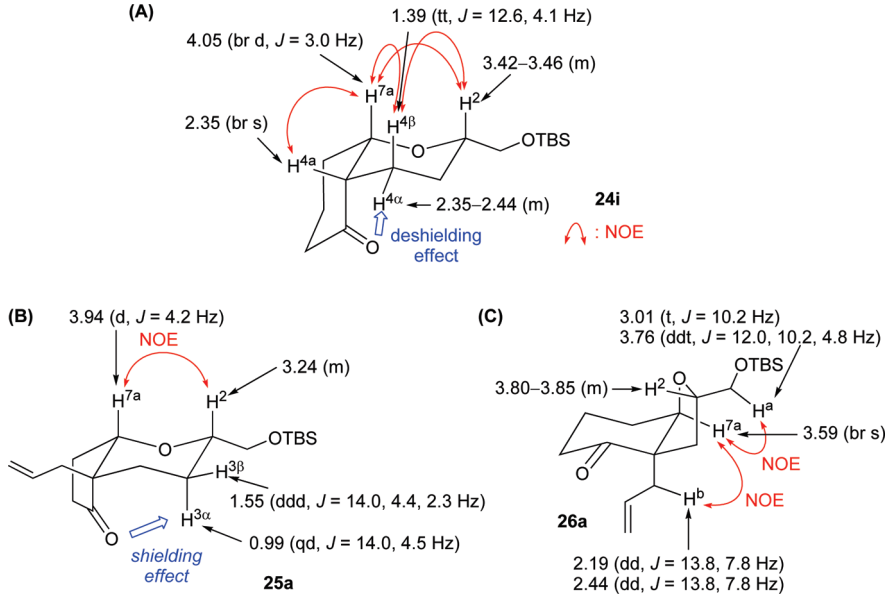


FIGURE 3. Selected data of ^1H NMR spectra and observed NOE in **24i** (A), **25a** (B), and **26a** (C).

the carbonyl group. The relationship between H^2, $H^{4\beta}$, H^{4a}, and H^{7a} can be determined as all cis by observation of the nuclear Overhauser effect (NOE; Figure 3A).

The configuration between H^{7a} and H^2 in **25a** was determined as cis by observation of the NOE, and that between H^{7a} and the allyl group was also estimated as cis by the chemical shift of $H^{3\alpha}$ observed at unusually high field (0.99 ppm), which was caused by the shielding effect of the carbonyl group (Figure 3B).

On the other hand, the stereochemistry in **26a** was determined by clearly observed NOE (Figure 3C). It is noteworthy that the stereochemistry between the TBS-oxymethyl group and the allyl group at C4a in **25a** was the trans configuration, whereas that in **26a** was cis. We discuss an explanation for this difference and a plausible mechanism for both substrates in section 2.4.

3. Application to the Synthesis of a Trichothecene Skeleton. Trichothecenes belong to the sesquiterpene family, and some

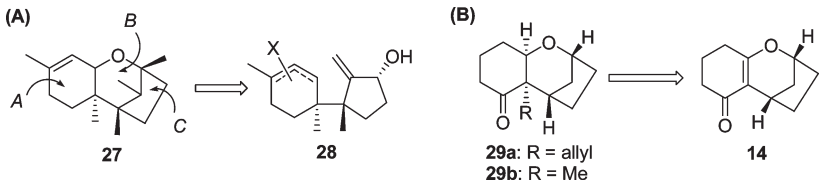
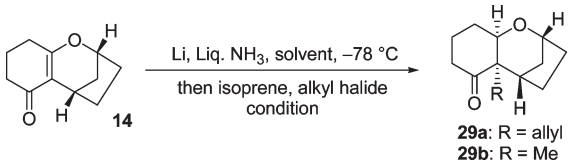


FIGURE 4. (A) Trichothecene skeleton **27** and its synthetic precursor **28**. (B) Structure of the target molecules **29a** and **29b** and their precursor **14**.

TABLE 2. Diastereoselective Birch Reduction−Akylation Reaction of 14[a]



entry	alkyl halide	solvent	alkylation conditions	yield (%)
1	allyl bromide	THF	−78 °C, 40 min, and then −33 °C, 4 h	44 (**29a**)
2	allyl iodide	THF	−78 °C, 1.5 h	49 (**29a**)
3		Et_2O	−78 °C, 2.3 h	49 (**29a**)
4	methyl iodide	THF	−78 °C, 1.5 h	45 (**29b**)

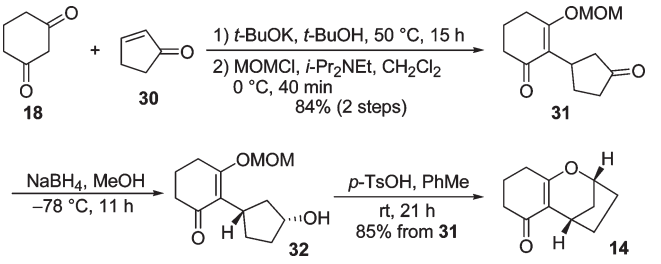
[a] **29a** and **29b** were isolated as a single diastereomer.

of them are known to possess antitumor activity.[18] The key structural feature of the trichothecene skeleton **27** is having a tricyclic structure, in which the stereochemistries of the three rings are all in the cis configuration (Figure 4). One frequently found strategy for the synthesis of trichothecenes is A and C ring formation with stereoselective functionalization (e.g., **28**), followed by ring closure to construct the B ring (Figure 4A).[19]

For application of the reductive−alkylation reaction described above, we assumed the compounds **29a** and **29b** to be the trichothecene skeleton, which could be synthesized from tricyclic β-alkoxy-α,β-unsaturated ketone **14** (Figure 4B). The key features in our approach are that (i) there are no published studies using reductive−alkylation for constructing a trichothecene skeleton to our knowledge and (ii) the correct stereochemistry for the trichothecene skeleton may be obtained by use of the reductive−alkylation method for more rigid substrates than the previously examined compounds like **2b**, **12b**, and **13b**.

The synthesis of **14** was started from 1,3-cyclohexanedione (**18**) and 2-cyclopentenone (**30**). The Michael addition reaction of **18** to **30** in the presence of *t*-BuOK in *t*-BuOH, followed by protection of the enol with the MOM group under standard conditions, provided the desired **31** at a yield of 84% (two steps). The use of *t*-BuOK in *t*-BuOH is superior to that of NaH in *N*,*N*-dimethylformamide (DMF) in terms of reproducibility. The reduction of the ketone on the cyclopentane ring was conducted by $NaBH_4$ in methanol at −78 °C, which gave the alcohol **32** as the sole product. Acid treatment of **32** in toluene at room temperature gave **14** at a yield of 85% from **31** (Scheme 4). Expectedly, the hydride attack to the ketone **31** would occur from the less hindered β-face to give a cis configuration between C1−OH and the C3 substitutent. The stereochemistry was confirmed by the result of the formation of tricyclic **14** by acidic treatment.

SCHEME 4. Synthesis of 14 from 18 and 30



The results of the reductive−alkylation reaction of **14** are summarized in Table 2. In all cases, isoprene was added to quench the excess amount of lithium before treatment with an alkyl halide. In the case of **14**, allyl iodide gave slightly better yields than allyl bromide [Table 2, entries 1 (44%) vs 2 (49%)], and the methyl group could also be introduced at the angular position [Table 2, entry 4 (45%)]. The solvent did not affect the yield of the product [Table 2, entries 2 (49%) vs 3 (49%)]. Although all of the yields in Table 2 are moderate because of the production of some unidentified byproduct, the isolable alkylated product was obtained as a single diastereomer. The stereochemistry of **29a** was determined by a NOE experiment, as shown in Figure 5, and that of **29b** was confirmed by analogy with the ^{1}H NMR spectrum.

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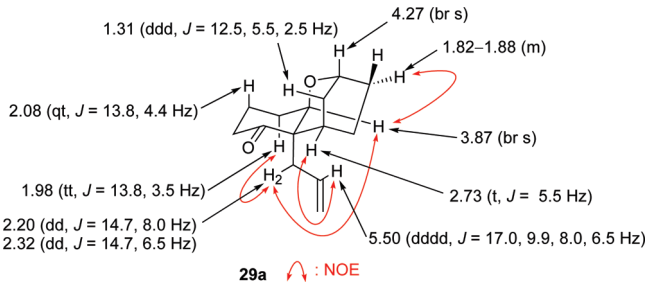


FIGURE 5. Selected data of the ^{1}H NMR spectrum and observed NOE in **29a**.

4. Plausible Mechanism for the Diastereoselective Reductive−Alkylation of Bi- and Tricyclic *β*-Alkoxy-α,*β*-unsaturated Ketone Derivatives. In our previous article, we proposed a possible mechanism for the expression of diastereoselectivity in the reductive−alkylation reaction of **2b**.[5] Namely, protonation may proceed from the dianione **33**, which might be the most stable conformer among the four possible structures, to produce the enolate. From the observed stereochemistry of **24**, one possible way for the alkylation to proceed is by approaching the allyl bromide from the equatorial direction in **34a**. However, we expect that this possibility is quite unlikely when we consider the stereoelectronic effect. Thus, we speculate that alkylation occurs after a flipping of the conformation from **34a** to **34b** and then proceeds from the *β* face (axial direction). The origin of the predominance of **34b** over **34a** is not yet clear, but one possible reason may be the stabilizing effect of the C−O antibonding orbital by ligation of the enolate *π* orbital (Scheme 5).

For the reactions of **12b** and **13b**, reaction pathways similar to that of Scheme 5 can be considered. These are shown in Scheme 6.

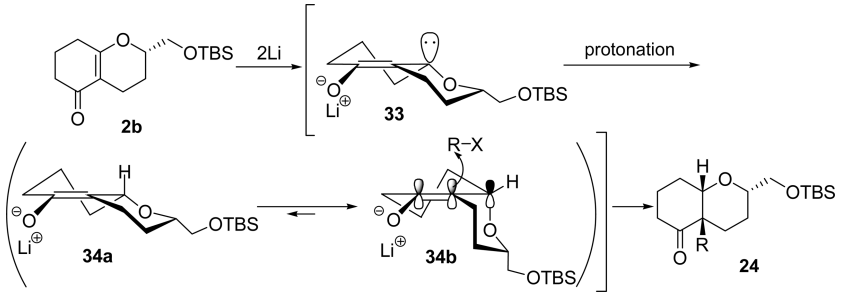
The dianiones **35a** and **37a**, which are the most stable among the possible conformers, e.g., **35b** or **37b**, protonate to produce the enolates **36a** and **38a**. These enolates flip to **36b** and **38b** in order to create a parallel C−O bond with the *π* bond of the enolate. The alkylation occurs from the axial direction, i.e., from the *β* face for **36b** and from the α face for **38b**, to give **25** and **26**, respectively (Scheme 6). Although the relative stereochemistry between the TBS-oxymethyl group and the introduced alkyl group is trans for **25** and cis for **26**, these difference can be reasonably accounted for by the plausible mechanism described above.

Furthermore, the diastereoselective production of **29** from **14** can be reasonably explained by the similar mechanism, including the conformational change from **40a** to **40b** (Scheme 7).

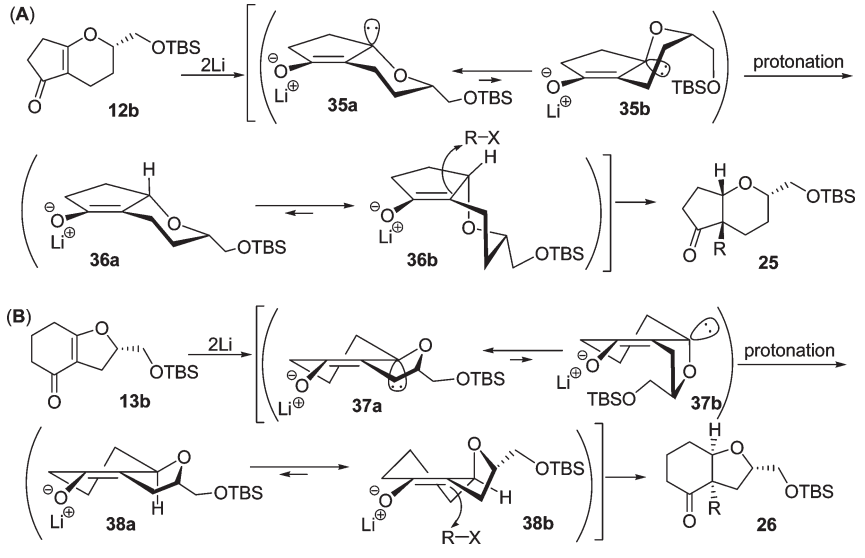
Conclusion

We were able to demonstrate diastereoselective Birch reduction−alkylation reactions by the bicyclic *β*-alkoxy-α,

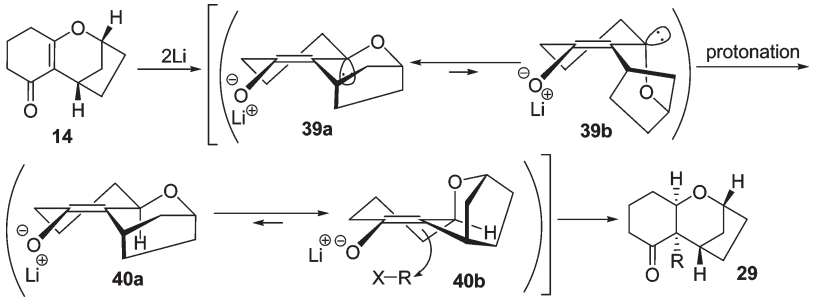
SCHEME 5. Plausible Mechanism for the Diastereoselective Reductive−Alkylation Reaction of 2b



SCHEME 6. Plausible Mechanism for Diastereoselective Reductive−Alkylation Reactions of 12b and 13b



SCHEME 7. Plausible Mechanism for the Diastereoselective Reductive−Alkylation Reaction of 14



β-unsaturated carbonyl compounds **2b**, **12b**, and **13b** and tricyclic analogue **14**. Although the diastereoselectivity varied depending on the structures of the substrates, i.e., **2b** and **12b** gave the trans configuration between the TBS-oxymethyl group and the substituent at the angular position and **13b** gave the cis configuration, the selectivity could be accounted for by the same reaction pathways. Namely, the stereochemistry at the β position of β-alkoxy-α,β-unsaturated carbonyl compounds is induced by the stereochemistry of the TBS-oxymethyl group and that at the α position is controlled as cis to the β position for all starting materials. The product from **14** corresponds to the trichothecene skeleton. Application of this methodology to the synthesis of biologically active compounds is underway in our laboratory.

Experimental Section

General Procedure for the Birch Reduction−Alkylation Reaction. Under an argon atmosphere, lithium wire was added to liquid NH_3 at −78 °C, which was distilled over sodium. After stirring for 10−30 min at −78 °C, a solution of the substrate in anhydrous tetrahydrofuran (THF) or diethyl ether was added to the mixture. For entries 3−10 and 13 in Table 1 and all entries in Table 2, isoprene was added to the mixture. Alkyl halide was added to the mixture, and the stirring was continued for the time listed in Tables 1 and 2 at −78 °C. A saturated aqueous NH_4Cl solution was added to the mixture, and NH_3 was evaporated at 40 °C. The aqueous layer was extracted with ethyl acetate for reactions in Table 1 or diethyl ether in all entries in Table 2. The combined organic solution was washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude product.

(2*S*,4a*S*,8a*S*)-2-(*tert*-Butyldimethylsilanyloxymethyl)-4a-methyloctahydrochromen-5-one (24b; Table 1, Entry 4). According to the general procedure, **2b** (26.7 mg, 90.1 μmol) was reduced by lithium (3.6 mg, 0.519 mmol) in liquid NH_3 (5 mL) and anhydrous THF (1 mL). After the addition of isoprene (0.2 mL, 2.00 mmol), methyl iodide (0.1 mL, 1.61 mmol) was reacted at −78 °C for 40 min. The crude product upon workup was chromatographed on silica gel [ethyl acetate−hexane (1:39)] to afford **24b** (19.8 mg, 70%) as a colorless oil: $[\alpha]^{27}_D$ −37.1 (c = 1.03, $CHCl_3$); IR ν (neat, cm^{-1}) 1711, 1462, 1254, 1134, 1092, 837; ^1H NMR (600 MHz, $CDCl_3$) δ 0.008 (3H, s), 0.010 (3H, s), 0.85 (9H, s), 1.04 (1H, td, J = 13.5, 4.3 Hz), 1.08 (3H, s), 1.27 (1H, tdd, J = 13.5, 11.5, 4.0 Hz), 1.45 (1H, ddt, J = 13.5, 4.3, 2.6 Hz), 1.76−1.86 (2H, m), 2.03 (1H, tdd, J = 13.6, 4.2, 2.4 Hz), 2.10 (1H, qt, J = 13.6, 4.3 Hz), 2.24 (1H, ddt, J = 15.3, 4.3, 2.2 Hz), 2.36 (1H, ddd, J = 13.5, 4.0, 2.6 Hz), 2.50 (1H, ddd, J = 15.3, 13.6, 6.6 Hz), 3.37 (1H, dddd, J = 11.5, 6.2, 5.2, 2.6 Hz), 3.42 (1H, dd, J = 10.5, 5.2 Hz), 3.56 (1H, dd, J = 10.5, 6.2 Hz), 3.61 (1H, t, J = 2.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.3, −5.1, 18.4, 20.9, 24.4, 25.6, 25.9, 26.6, 31.9, 37.9, 48.2, 66.8, 78.9, 83.0, 214.3; MS m/z 297 (M^+ − Me, 1%), 255 (M^+ − t-Bu, 65%), 171 (100%). HRMS. Calcd for $C_{13}H_{23}O_3Si$: 255.1416. Found: 255.1404.

(2*S*,4a*R*,8a*S*)-4a-Benzyl-2-(*tert*-butyldimethylsilanyloxymethyl)octahydrochromen-5-one (24c; Table 1, Entry 5). According to the general procedure, reduction of **2b** (19.6 mg, 66.1 μmol) was performed by lithium (4.3 mg, 0.620 mmol) in liquid NH_3 (5 mL) and anhydrous THF (1 mL). After the addition of isoprene (0.1 mL, 1.00 mmol), benzyl bromide (0.1 mL, 0.841 mmol) was reacted at −78 °C for 1 h. The crude product upon workup was purified by silica gel column chromatography [ethyl acetate−hexane (1:39)] to afford **24c** (13.7 mg, 53%) as a colorless oil: $[\alpha]^{26}_D$ −53.6 (c = 0.69, $CHCl_3$); IR ν (neat, cm^{-1}) 1707, 1128, 1088, 837; ^1H NMR (600 MHz, $CDCl_3$) δ 0.018 (3H, s), 0.021 (3H, s), 0.86 (9H, s), 1.08 (1H, td, J = 13.0, 4.2 Hz), 1.21 (1H, td, J = 13.0, 4.2 Hz), 1.43 (1H, ddt, J = 13.0, 4.2, 2.3 Hz), 1.90−1.96 (2H, m), 2.06 (1H, dt, J = 13.0, 4.2 Hz), 2.21 (1H, qt, J = 13.4, 4.5 Hz), 2.26−2.33 (1H, m), 2.38−2.43 (1H, m), 2.67 (1H, d, J = 13.8 Hz), 2.79 (1H, ddd, J = 14.7, 13.4, 6.6 Hz), 3.09 (1H, d, J = 13.8 Hz), 3.30−3.36 (1H, m), 3.41 (1H, dd, J = 10.7, 5.1 Hz), 3.56 (1H, dd, J = 10.7, 6.0 Hz), 3.77 (1H, br s), 6.98−7.00 (2H, m), 7.19−7.27 (3H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.3, −5.2, 18.4, 21.3, 25.1, 25.9, 26.6, 28.8, 38.6, 43.0, 52.5, 66.7, 78.7, 82.3, 126.8, 128.1, 129.8, 135.8, 212.8; MS m/z 373 (M^+ − Me, 2%), 331 (M^+ − t-Bu, 100%), 313 (9%), 247 (30%), 197 (31%), 91 (90%). HRMS. Calcd for $C_{19}H_{27}O_3Si$: 331.1730. Found: 331.1732.

(2*S*,4a*R*,7a*S*)-4a-Allyl-2-(*tert*-butyldimethylsilanyloxymethyl)-hexahydrocyclopenta[*b*]pyran-5-one (25a; Table 1, Entry 11). According to the general procedure, reduction of **12b** (92 mg, 0.326 mmol) was performed by lithium (9.4 mg, 1.35 mmol) in liquid NH_3 (5 mL) and anhydrous THF (1 mL). Allyl bromide (0.58 mL, 6.72 mmol) was reacted at −78 °C for 1.5 h. The crude product upon workup was purified by silica gel column chromatography [ethyl acetate−hexane (1:4z)] to afford **25a** (63 mg, 58%) as a colorless oil, and **12b** (6 mg, 6%) was recovered from the later fractions. **25a**: $[\alpha]^{27}_D$ = +22.2 (c = 0.46, $CHCl_3$); IR ν (neat, cm^{-1}) 1742, 1094, 837; ^1H NMR (600 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.87 (9H, s), 0.99 (1H, qd, J = 14.0, 4.5 Hz), 1.48 (1H, td, J = 13.8, 4.8 Hz), 1.55 (1H, ddd, J = 14.0, 4.4, 2.3 Hz), 1.97−2.04 (3H, m), 2.10−2.13 (1H, m), 2.14−2.19 (1H, m), 2.33 (1H, dd, J = 19.2, 10.2 Hz), 2.41 (1H, dd, J = 19.2, 10.2 Hz), 3.24 (1H, m), 3.41 (1H, dd, J = 10.8, 4.8 Hz), 3.58 (1H, dd, J = 10.8, 6.0 Hz), 3.94 (1H, d, J = 4.2 Hz), 5.04 (1H, d, J = 16.8 Hz), 5.10 (1H, d, J = 10.2 Hz), 5.68 (1H, ddd, J = 16.8, 10.2, 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.3, −5.2, 18.3, 25.2, 25.6, 25.8, 25.9, 33.8, 38.7, 52.4, 66.5, 76.6, 81.1, 118.6, 132.1, 219.0; MS m/z 267 (M^+ − t-Bu, 100%). HRMS. Calcd for $C_{14}H_{23}O_3Si$: 267.1416. Found: 267.1413.

(2*S*,4a*S*,7a*S*)-2-(*tert*-Butyldimethylsilanyloxymethyl)-4a-methylhexahydrocyclopenta[*b*]pyran-5-one (25b; Table 1, Entry 12). According to the general procedure, **12b** (95 mg, 0.336 mmol) was reduced by lithium (9.1 mg, 1.30 mmol) in liquid NH_3 (5 mL) and anhydrous THF (1 mL). Methyl iodide (0.65 mL, 6.51 mmol) was reacted at −78 °C for 1.5 h. The crude product upon workup was purified by preparative TLC developed with ethyl acetate−hexane (1:4) to afford **25b** (66 mg, 68%) as a

colorless oil, and **12b** (7 mg, 7%) was recovered. **25b**: $[\alpha]^{26}_D$ = +39.3 (c = 0.40, $CHCl_3$); IR ν (neat, cm^{-1}) 1744, 1097, 837; ^1H NMR (600 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 0.92 (3H, s), 0.94−1.02 (1H, m), 1.40 (1H, td, J = 13.2, 4.8 Hz), 1.52 (1H, dt, J = 13.2, 2.4 Hz), 2.01 (1H, ddd, J = 13.8, 9.0, 2.4 Hz), 2.15 (1H, m), 2.20 (1H, ddd, J = 13.8, 4.2, 2.4 Hz), 2.31−2.42 (2H, m), 3.28 (1H, m), 3.42 (1H, dd, J = 10.8, 5.4 Hz), 3.59 (1H, dd, J = 10.8, 5.4 Hz), 3.85 (1H, d, J = 3.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.3, −5.2, 18.4, 21.6, 25.5, 25.8, 25.9, 28.8, 33.8, 49.1, 66.6, 76.8, 82.8, 220.3; MS m/z 283 (M^+ − Me, 2%), 241 (M^+ − t-Bu, 100%), 223 (26%), 149 (39%). HRMS. Calcd for $C_{15}H_{27}O_3Si$: 283.1729. Found: 283.1726. Calcd for $C_{12}H_{21}O_3Si$: 241.1260. Found: 241.1243.

(2*S*,3a*R*,7a*R*)-3a-Allyl-2-(*tert*-butyldimethylsilanyloxymethyl)-hexahydrobenzofuran-4-one (26a; Table 1, Entry 13). According to the general procedure, reduction of **13b** (88 mg, 0.312 mmol) was performed by lithium (8.7 mg, 1.25 mmol) in liquid NH_3 (5 mL) and anhydrous THF (1 mL). After the addition of isoprene (0.65 mL, 6.51 mmol), allyl bromide (0.54 mL, 6.24 mmol) was reacted at −78 °C for 1.5 h. The crude product upon workup was purified by preparative TLC developed with ethyl acetate−hexane (1:9) to afford **26a** (53 mg, 52%) as a colorless oil: $[\alpha]^{23}_D$ = −44.9 (c = 1.06, $CHCl_3$); IR ν (neat, cm^{-1}) 1708, 1099, 85, 837, 775; ^1H NMR (600 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 0.99 (1H, t, J = 12.0 Hz), 1.86 (2H, m), 2.05−2.12 (2H, m), 2.19 (1H, dd, J = 13.8, 7.8 Hz), 2.27−2.30 (1H, m), 2.44 (1H, dd, J = 13.8, 7.8 Hz), 2.46−2.52 (1H, m), 2.55 (1H, dd, J = 12.0, 4.8 Hz), 3.01 (1H, t, J = 10.2 Hz), 3.59 (1H, br s), 3.76 (1H, ddt, J = 12.0, 10.2, 4.8 Hz), 3.80−3.85 (1H, m), 5.06 (1H, d, J = 16.8 Hz), 5.08 (1H, d, J = 10.2 Hz), 5.59 (1H, ddt, J = 16.8, 10.2, 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.8, −4.6, 18.1, 21.1, 25.9, 26.0, 38.2, 38.6, 41.5, 53.6, 64.2, 73.1, 81.7, 118.8, 131.4, 212.2; MS m/z 267 (M^+ − t-Bu, 52%), 131 (29%), 117 (100%). HRMS. Calcd for $C_{14}H_{23}O_3Si$: 267.1416. Found: 267.1426.

(2*S*,3a*R*,7a*S*)-2-(*tert*-Butyldimethylsilanyloxymethyl)-3a-methyloctahydroinden-4-one (26b; Table 1, Entry 14). According to the general procedure, **13b** (46 mg, 0.16 mmol) was reduced by lithium (4.6 mg, 0.65 mmol) in liquid NH_3 (5 mL) and anhydrous THF (0.5 mL). Methyl iodide (0.32 mL, 3.26 mmol) was reacted at −78 °C for 1.5 h. The crude product upon workup was purified by preparative TLC developed with ethyl acetate−hexane (1:4) to afford **26b** (12 mg, 25%) as a colorless wax, and **13b** (16 mg, 35%) was recovered. **26b**: $[\alpha]^{26}_D$ = −54.8 (c = 0.3, $CHCl_3$); IR ν (neat, cm^{-1}) 1713, 1096, 1070, 837, 775; ^1H NMR (600 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 0.98 (1H, dd, J = 12.6, 10.8 Hz), 1.14 (3H, s), 1.81−1.89 (2H, m), 2.02−2.09 (2H, m), 2.25−2.28 (1H, m), 2.55 (2H, ddd, J = 12.6, 4.8, 2.4 Hz), 3.03 (1H, t, J = 10.8 Hz), 3.52 (1H, s), 3.75 (1H, ddd, J = 15.0, 10.2, 4.8 Hz), 3.84 (1H, ddd, J = 10.8, 5.4, 2.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.8, −4.7, 18.1, 21.1, 24.4, 25.9, 26.3, 37.7, 41.7, 50.0, 64.0, 73.3, 83.1, 213.5; MS m/z 298 (M^+, 2%), 241 (M^+ − t-Bu, 11%), 117 (100%). HRMS. Calcd for $C_{16}H_{30}O_3Si$: 298.1964. Found: 298.1988. Calcd for $C_{12}H_{21}O_3Si$: 241.1260. Found: 241.1255.

(1*S,2*R**,7*R**,9*R**)-2-Allyl-8-oxatricyclo[7.2.1.0^{2,7}]dodecan-3-one (29a; Table 2, Entry 2).** According to the general procedure, **14** (26.9 mg, 0.151 mmol) was reduced by lithium (4.2 mg, 0.604 mmol) in liquid NH_3 (5 mL) and anhydrous THF (2 mL). After the addition of isoprene (0.151 mL, 1.51 mmol), allyl iodide (0.276 mL, 3.02 mmol) was reacted at −78 °C for 1.5 h. The crude product upon workup was purified by silica gel column chromatography [ethyl acetate−hexane (1:19)] to afford **29a** (16.3 mg, 49%) as a colorless solid: mp 87−89 °C (colorless needles from hexane); IR ν (neat, cm^{-1}) 1699, 1614, 1454, 1069, 1007; ^1H NMR (600 MHz, $CDCl_3$) δ 1.31 (1H, ddd, J = 12.5, 5.5, 2.5 Hz), 1.59−1.80 (6H, m), 1.82−1.88 (1H, m), 1.98 (1H, tt, J = 13.8, 3.5 Hz), 2.08 (1H, qt, J = 13.8, 4.4 Hz), 2.20 (1H, dd, J = 14.7, 8.0 Hz), 2.32 (1H, dd, J = 14.7, 6.5 Hz), 2.34−2.42 (2H, m), 2.73 (1H, t, J = 5.5 Hz), 3.87 (1H, br s), 4.27 (1H, br s), 4.97 (1H, dd, J = 17.0, 1.0 Hz), 5.03 (1H, dt, J = 9.9, 1.0 Hz), 5.50 (1H, dddd, J = 17.0, 9.9, 8.0, 6.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.1, 22.6, 26.8, 28.9, 36.4, 36.8, 37.9, 39.4, 55.1, 74.7, 76.3, 118.0, 131.7, 212.8; MS m/z 220 (M^+, 24%), 192 (7%), 178 (100%), 163 (11%), 149 (33%). HRMS. Calcd for $C_{14}H_{20}O_2$: 220.1464. Found: 220.1462. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.24; H, 9.14.

(1*S,2*R**,7*R**,9*R**)-2-Methyl-8-oxatricyclo[7.2.1.0^{2,7}]dodecan-3-one (29b; Table 2, Entry 4).** According to the general procedure, **14** (98.3 mg, 0.552 mmol) was reduced by lithium (15.3 mg, 2.21 mmol) in liquid NH_3 (15 mL) and anhydrous THF (6 mL). After the addition of isoprene (0.552 mL, 5.52 mmol), methyl iodide (0.685 mL, 11.0 mmol) was reacted at −78 °C for 1.5 h. The crude product upon workup was purified by silica gel column chromatography [ethyl acetate−hexane (1:19)] to afford a mixture of **29b** (48.2 mg, 45%) as a colorless oil: IR ν (neat, cm^{-1}) 1705, 1456, 1202, 1080, 1061, 1013; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, s), 1.29 (1H, ddd, J = 14.0, 6.8, 3.2 Hz), 1.61−1.98 (8H, m), 2.01−2.14 (1H, m), 2.33 (1H, ddt, J = 15.9, 4.6, 2.3 Hz), 2.46 (1H, ddd, J = 15.9, 13.6, 6.0 Hz), 2.61 (1H, br t, J = 4.8 Hz), 3.83 (1H, br t, J = 3.0 Hz), 4.28 (1H, br t, J = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 22.6, 23.2, 26.7, 29.0, 37.3, 38.7, 40.5, 51.4, 74.6, 76.3, 215.1; MS m/z 194 (M^+, 100%), 179 (7%), 166 (13%), 150 (22%), 138 (49%), 123 (96%). HRMS. Calcd for $C_{12}H_{18}O_2$: 194.1307. Found: 194.1295.

Supporting Information Available: Experimental procedures, compound characterization, and analytical data (specific rotation, ^1H and ^{13}C NMR, MS, and HRMS) for compounds **12b**, **13a**, **13b**, **14**, **15**, **24a**, **24i**, and **31**, copies of ^1H and ^{13}C NMR spectra of all new compounds and **24a**, and copies of NOESY spectra of **24i**, **25a**, **26a**, and **29a**. This material is available free of charge via the Internet at http://pubs.acs.org.