Construction of the Tricyclo[5.3.1.0^{1,5}]undecane System by a Novel Tandem Pinacol Rearrangement-Ene Strategy: A Formal Total Synthesis of (±)-Perhydrohistrionicotoxin

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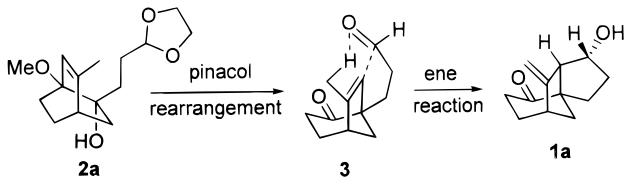
Histrionicotoxin derivatives have long been attractive targets for synthetic chemists as a result of their useful neurophysical properties, low natural abundance, and the unique structural features of the azaspiro[5.5]undecane ring system. Utilizing our tandem pinacol rearrangement-ene strategy and regiospecific Baeyer−Villiger oxidation as key steps, we have successfully synthesized an advanced synthetic intermediate, spiro[5.4]decane **4**, which has previously been converted to (±)-perhydrohistrionicotoxin (**5b**). Pinacol rearrangement of simple Diels−Alder derived bicyclo[2.2.2]-octene system **2a**, followed by an ene reaction, led to the efficient formation of the highly fuctionalized tricyclo[5.3.1.0^{1,5}]undecane system **1a**. This tricyclic system **1a** was selectively transformed into spiro[5.4]decane system **4** via a regiospecific Baeyer−Villiger oxidation reaction. We also report the results of systematic studies of Baeyer−Villiger oxidation reactions of tricyclo[5.3.1.0^{1,5}]-undecanone systems to elucidate the origin of the regioselectivity of this process.

Introduction

The application of tandem organic chemical reactions is often a very efficient strategy for the construction of structurally and stereochemically complex structures from relatively simple starting materials.[1] We envisaged that a novel tandem pinacol rearrangement-ene reaction[2,3] on an appropriate bicyclo[2.2.2]octene system might be useful for the formation of the structurally complex tricyclo[5.3.1.0^{1,5}]undecane system. Construction of the tricyclo[5.3.1.0^{1,5}]undecane system, which constitutes the basic carbon framework of natural products such as cedranes, has been a continuous challenge to synthetic organic chemists and has led to the development of diverse synthetic strategies.[4] Thus, we believed pinacol rearrangement of simple Diels−Alder derived bicyclo[2.2.2]octene system **2a**,[5] followed by an ene reaction, would lead to the efficient formation of highly fuctionalized tricyclo[5.3.1.0^{1,5}]undecane system **1a** via the intermediacy of bicyclo[3.2.1]octene derivative **3** as illustrated in Scheme 1.

Scheme 1



We also envisaged that the tricyclo[5.3.1.0^{1,5}]undecane system **1** could be converted to the azaspiro[5.5]undecane ring system, which is the basic skeleton of histrionicotoxin (**5a**) and its saturated congener, perhydrohistrionicotoxin (**5b**). The azaspirocycle alkaloid (−)-histrionicotoxin (**5a**), isolated from skin extracts of the brightly colored poison-arrow frog *Dendrobates histrionicus* found in Colombia, is a potent noncompetitive blocker of nicotinic receptor-gated channels.[6] The significant interest of histrionicotoxin derivatives stems from their remarkable neurophysical properties,[7] their low natural abundance,[7] and their unique structural features containing the azaspiro[5.5]undecane ring system. These alkaloids have been attractive and popular targets for synthetic chemists for many years.[8] In this paper,[9] we

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(1) For an excellent review, see: Ho, T. L. *Tandem Reactions in Organic Synthesis*; Wiley-Interscience: New York, 1992.

(2) We appreciate a referee's suggestion that the second reaction of our tandem process, particularly in a case such as **2a** where a five-membered ring is formed, is more properly called a Prins reaction rather than an ene reaction.

(3) For a tandem Prins-pinacol rearrangement process, see: (a) Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem*. **1997**, *62*, 6376. (b) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927 and references cited.

(4) Chen, Y.; Lin, W. *Tetrahedron Lett*. **1992**, *33*, 1749 and references cited.

(5) Pinacol rearrangement of a Diels−Alder derived bicyclo[2.2.2]-octene has previously been exploited in the syntheses of various natural products: (a) Monti, S. A.; Chen, S.; Yang, Y.; Yuan, S.; Bourgeois, O. P. *J. Org. Chem*. **1978**, *43*, 4062. (b) Monti, S. A.; Dean, T. R. *J. Org. Chem*. **1982**, *47*, 2679 and references cited.

(6) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Wikop, B. *Proc. Natl. Acad. Sci. U.S.A*. **1971**, *68*, 1870.

(7) (a) Daly, J. W. *J. Nat. Prod*. **1998**, *61*, 162. (b) Albuquerque, E. X.; Kuba, K.; Daly, J. W. *J. Pharmacol. Exp. Therap*. **1974**, *189*, 513.

(8) (a) For a recent synthesis of (−)-histrionicotoxin by using a tandem process as a key step, see Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem. Soc*. **1999**, *121*, 4900. (b) For a recent synthesis of perhydrohistrionicotoxin, see; Luzzio, F. A.; Fitch, R. W. *J. Org. Chem*. **1999**, *64*, 5485 and references cited. (c) For a good review with citations to recent work, see: Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907. (d) For a comprehensive review on studies before 1989, see: Kotera, M. *Bull. Soc. Chim. Fr*. **1989**, 370.

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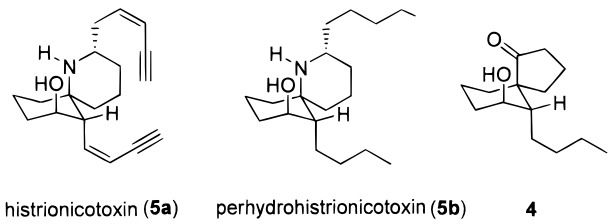
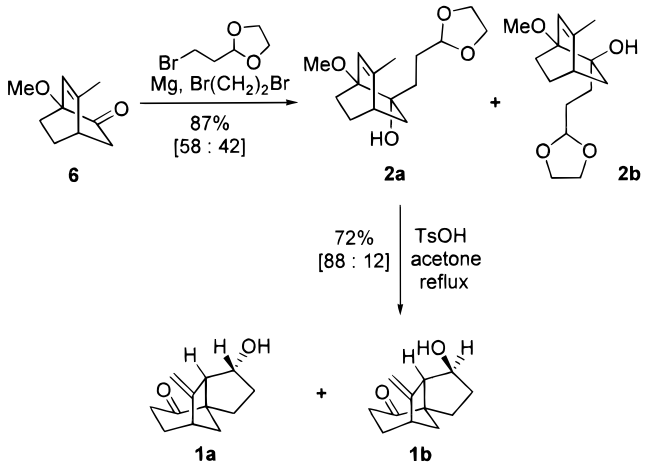


Figure 1.

Scheme 2



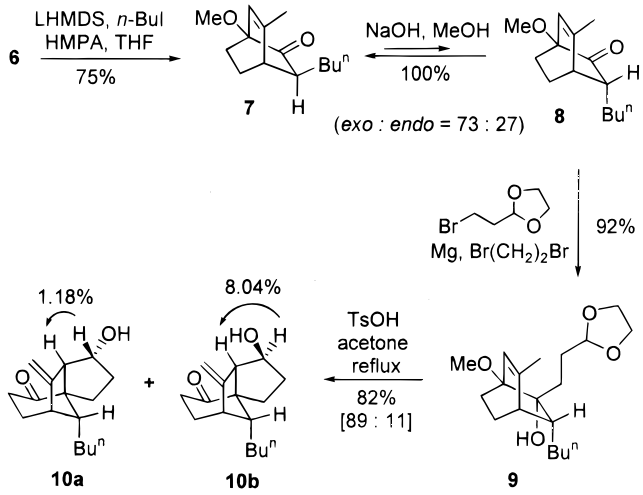
describe full details of the stereoselective synthesis of an advanced intermediate spiro[5.4]decane **4**, which has been previously converted to (±)-perhydrohistrionicotoxin (**5b**) by Ibuka[10a] and Corey,[10b] employing tandem pinacol rearrangement-ene reaction and a regioselective Baeyer–Villiger oxidation as key steps.

Results and Discussion

To first examine the feasibility of the proposed tandem pinacol rearrangement-ene reaction, we prepared *endo* alcohol **2a** in which the migrating olefinic bridge and hydroxyl group assume a stereoelectronically favorable antiperiplanar arrangement (Scheme 2). Treatment of readily available bicyclo[2.2.2]octenone **6**[5a] with 2-(2-bromoethyl)-1,3-dioxolane and magnesium turnings in THF[11] led to the formation of a readily separable mixture of *endo* **2a** and *exo* alcohol **2b** in a 58:42 ratio (87% total yield) as indicated in Scheme 2. As we had planned, *endo* alcohol **2a** could be smoothly transformed to the desired tricyclic ketones **1a** and **1b** in a ratio of 88:12 (72% total yield) upon treatment with *p*-TsOH (1.2 equiv) in refluxing acetone for 11 h via an efficient novel tandem pinacol rearrangement-ene reaction.[12,13]

On the basis of these results, a formal total synthesis of (±)-perhydrohistrionicotoxin (**5b**) was undertaken from ketone **6**.[5a] Alkylation of ketone **6** by treatment with LHMDS and *n*-butyl iodide in THF containing HMPA at

Scheme 3



−78 to −20 °C produced a 75% yield of *exo* product **7** stereospecifically. Epimerization of *exo* isomer **7** with methanolic NaOH gave a chromatographically separable 73:27 equilibrium mixture of *exo* **7** and *endo* isomer **8** in quantitative yield. Treatment of bicyclic ketone **8**, secured in a large quantity by recycling of *exo* isomer **7**, with 2-(2-bromoethyl)-1,3-dioxolane derived Grignard reagent under Barbier conditions[11] led to the stereospecific formation of *endo* alcohol **9** in 92% yield. As with **2a**, compound **9** also underwent a facile tandem pinacol rearrangement-ene reaction to afford tricyclic intermediate **10a** and its epimeric alcohol **10b** in an 89:11 ratio (82% total yield) as shown in Scheme 3. The configurations at the carbinol carbon of **10a** and **10b** were firmly established by ^{1}H NMR NOE experiments as shown in Scheme 3.

We next turned to the conversion of the tricyclic intermediate **10a** to our target compound **4** for the synthesis of (±)-perhydrohistrionicotoxin (**5b**). To reduce the ketone functionality of tricyclic ketone **10a**, a Huang–Minlon modified[14] Wolff–Kishner reduction condition (NH_2NH_2, KOH, and ethylene glycol) was employed. Unfortunately, these standard reduction conditions provided not only the desired alkene **11** but also over-reduced compound **11′**.[15] However, we managed to efficiently obtain only the desired alkene **11** simply by adding 2-methylenepropane-1,3-diol (10 equiv) to the reaction mixture, suppressing the reduction of the double bond of product by trapping the diimide that is presumably generated. Ozonolysis of the resulting alkene **11** then furnished the corresponding ketone **12** in 51% overall yield for the two steps.

Among many conceivable synthetic schemes to arrive at the final product, we felt an ammonolysis-Hoffmann

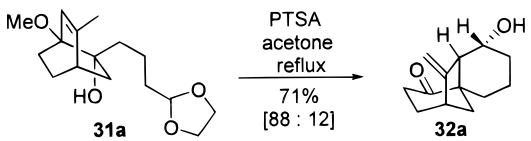
(9) Part of this work has been published in preliminary form, see: Kim, D.; Hong, S. W.; Park, C. W. *J. Chem. Soc., Chem. Commun.* **1997**, *21*, 2263.

(10) (a) Ibuka, T.; Mitsui, Y.; Hayashi, K.; Minakata, H.; Inubushi, Y. *Tetrahedron Lett.* **1981**, *22*, 4425. (b) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430.

(11) (a) Greiner, A. *Tetrahedron Lett.* **1989**, *30*, 3547. (b) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.

(12) Under these reaction conditions, *exo* alcohols including **2b** mainly furnished the antiperiplanar sp^3 carbon migrated pinacol rearrangement products (ca 50% yield) as noted by Monti.[5]

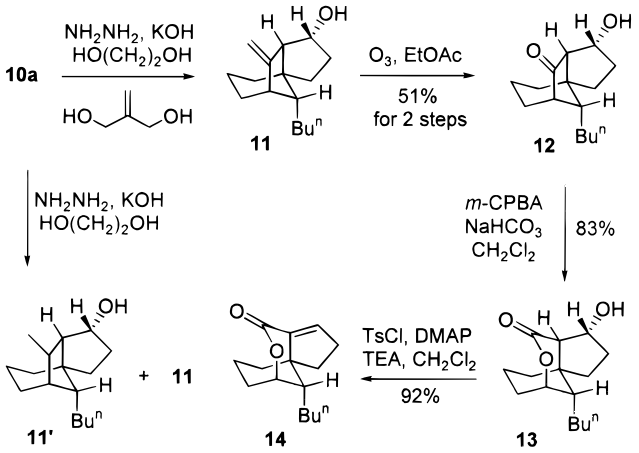
(13) Similarly, the application of a tandem pinacol rearrangement-ene reaction to the *endo* alcohol **31a** led to the desired six-membered tricyclic ketone **32a** as the major isomer (88:12).



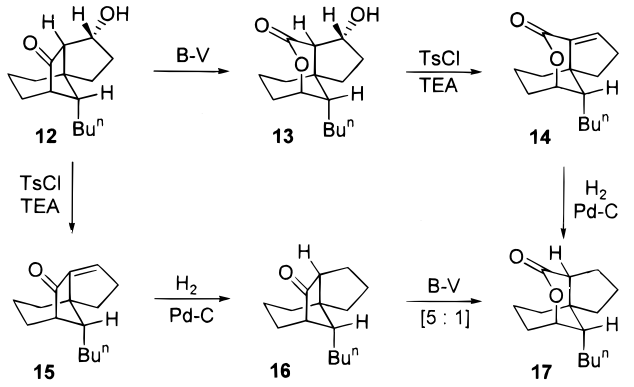
(14) (a) Huang-Minlon *J. Am. Chem. Soc.* **1946**, *68*, 2487. (b) Huang-Minlon *J. Am. Chem. Soc.* **1949**, *71*, 3301. (c) Matlin, A. R.; George, C. F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1986**, *108*, 3385.

(15) For an example of the reduction of an alkene during a modified Wolff–Kishner reduction, see: McIntosh, J. M. *Can. J. Chem.* **1979**, *57*, 2114.

Scheme 4



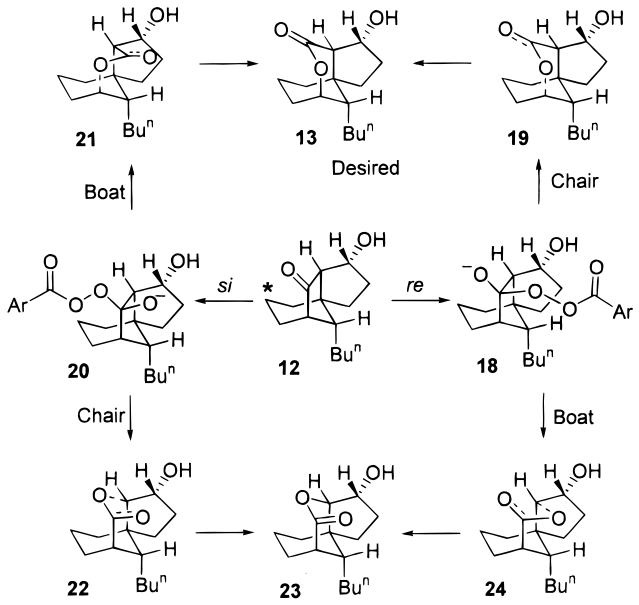
Scheme 5



rearrangement protocol on α,β-unsaturated-δ-lactone **14** would be most attractive (Scheme 4). We were pleased to find that hydroxy ketone **12** underwent a regiospecific Baeyer−Villiger reaction upon treatment with *m*-CPBA to give only lactone **13**, and subsequent elimination of the β-hydroxy group provided the desired α,β-unsaturated δ-lactone **14** (76% overall yield over two steps).

The migratory preference in the Baeyer−Villiger oxidation is generally related to the ability of the migrating group to accommodate a partial positive charge in the transition state.[16] Conformational, electronic, and steric effects also play an important role in determining which group migrates.[16] To elucidate the origin of the extremely high regioselectivity of the Baeyer−Villiger oxidation in the case of **12**, where the two possible migrating carbons are secondary, we investigated the Baeyer−Villiger oxidation of some typical tricyclo[5.3.1.$0^{1,5}$]undecanone systems as follows. First, to probe the possible polar effects[17] of the hydroxyl group on the regioselectivity, we prepared the corresponding deoxygenated ketone **16** from α,β-unsaturated ketone **15** by hydrogenation as shown in Scheme 5. Subjection of ketone **16** to our Baeyer−Villiger conditions yielded a 5:1 mixture of regioisomeric δ-lactones in favor of **17**, which was correlated with the hydrogenation product of **14**. The result of this experiment suggested that any polar effect by the hydroxyl group on the regioselectivity is insignificant. Therefore,

Scheme 6



we speculate that conformational effects in the transition state of the Baeyer−Villiger reaction might be the major influence in the regioselection.[16b]

The observed regioselectivity can best be rationalized by considering that peracid could attack on the *re* face of the carbonyl group of **12** to form the Criegee[18] tetrahedral intermediate **18**, where migration of the desired bond involves a stable chairlike transition state **19** (Scheme 6). Migration of the alternative bond, which yields the unobserved product **23**, goes through an unstable boatlike transition state **24**. The reverse is true in the case of nucleophilic attack on the *si* face (i.e., **12** to **20**). However, inspection of a molecular model of **12** clearly reveals that the *si* face of the carbonyl is much more hindered than the *re* face because of the indicated (*) methylene carbon, and thus nucleophilic attack on *si* face is unlikely. In the absence of the hydroxyl function (**16** to **17**), the boat route is slightly less favored over the chair one by a ratio of 1:5. Moreover, in the presence of the hydroxyl group (**12** to **13**), the boat **24** is further destabilized as a result of the polarity effect of the electronegative hydroxyl group, thus yielding only the desired lactone **13**.

To further support our hypothesis, we also performed the following experiments. Treatment of the α-TBS ether **25** with *m*-CPBA led to the formation of the desired δ-lactone **26** as shown in Scheme 7. However, the β-TBS ether **27**, where the *re* face of the carbonyl is hindered because of the bulky siloxy group, did not undergo the Baeyer−Villiger reaction under comparable conditions. This result supports our presumption that the hindered *si* face of the carbonyl is insulated from nucleophilic attack under our Baeyer−Villiger reaction conditions.

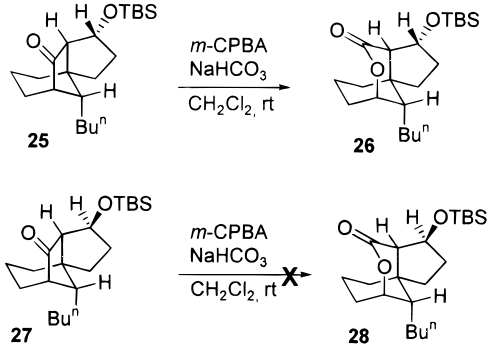
Our originally projected synthetic plan for further processing the key intermediate **4** by an ammonolysis-Hoffmann rearrangement protocol was thwarted by difficulties encountered in opening of the lactone **14** to the corresponding hydroxy-amide. To circumvent these problems, catalytic hydrogenation of the olefin functionality with 10% Pd−C and subsequent α-hydroxylation of the lactone **17** via the method of Davis[19] yielded α-hydroxyl

(16) (a) Krow, G. R. *Comprehensive Organic Synthesis*; Trost, B. M., Ed; Pergamon Press: New York, 1991; Vol. 7, p 673. (b) Krow, G. R. *Tetrahedron* **1981**, *37*, 2697.

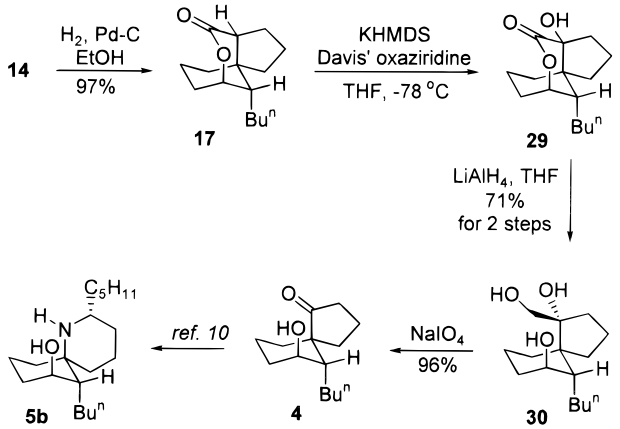
(17) Ho, T. L. *Polarity Control for Synthesis*; Wiley-Interscience: New York, 1991; p 353.

(18) Plesnicar, B. *Oxidation in Organic Chemistry*; Academic Press: New York, 1978; p 254.

Scheme 7



Scheme 8



lactone **29** as shown in Scheme 8. Finally, reductive opening of lactone **29** with $LiAlH_4$ in THF to the corresponding triol **30** (72% overall yield over two steps), followed by oxidative cleavage with $NaIO_4$ in acetone/H_2O (1:1) delivered in 96% yield the desired keto alcohol **4**, which is an advanced intermediate for the synthesis of (±)-perhydrohistrionicotoxin (**5b**). ^1H and ^{13}C NMR spectral data of compound **4** were in good agreement with those of an authentic sample kindly provided by Professors T. Ibuka[10a] and A. B. Smith, III.[20]

In conclusion, a formal total synthesis of (±)-perhydrohistrionicotoxin (**5b**) has been accomplished utilizing a novel tandem pinacol rearrangement-ene strategy and subsequent regiospecific Baeyer−Villiger oxidation as key steps. We also have investigated some systematic Baeyer−Villiger oxidation reactions of tricyclo[5.3.1.$0^{1,5}$]undecanones to spiro[5.4]decane systems to elucidate the origin of the regioselectivity. Currently, efforts are being made to apply this tandem pinacol rearrangement-ene strategy to the syntheses of some other natural products.

Experimental Section

2-[(1,3-Dioxolane-2-yl)ethyl]-4-methoxy-6-methylbicyclo-[2.2.2]oct-5-en-2-ol (2). A solution of ketone **6** (101.0 mg, 0.61 mmol) in dry THF (5 mL, 0.12 M) was slowly added dropwise onto magnesium turnings (52 mg, 2.14 mmol). To the mixture was added 2-(2-bromoethyl)-1,3-dioxolane (0.35 mL, 3.05 mmol) and a catalytic amount of 1,2-dibromoethane. After 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 7:1) to afford *endo* **2a** (82.6 mg, 50%) and *exo* alcohol **2b** (59.8 mg, 37%). ***endo*-Alcohol 2a:** ^1H NMR (pyridine-d_5, 300 MHz) δ 5.89 (s, 1H), 4.91 (t, J = 4.8 Hz, 1H), 3.87−3.80 (m, 2H), 3.76−3.58 (m, 2H), 3.31 (s, 3H), 2.34−2.16 (m, 4H), 2.01−1.89 (m, 1H), 1.82−1.75 (m, 1H), 1.67−1.62 (m, 6H), 1.60−1.31 (m, 2H); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 141.8, 126.2, 105.7, 83.8, 78.0, 64.9, 51.3, 41.0, 36.5, 33.3, 28.1, 24.9, 23.3, 20.1; IR (neat) 3445, 2936, 1093 cm^{-1}; HRMS ($M^+ - H$) m/z calcd for $C_{15}H_{23}O_4$ 267.1596, found 267.1600. ***exo*-Alcohol 2b:** ^1H NMR (pyridine-d_5, 300 MHz) δ 6.01 (s, 1H), 4.95 (br t, J = 4.8 Hz, 1H), 4.30 (s, 1H), 3.94−3.79 (m, 2H), 3.77−3.66 (m, 2H), 3.33 (s, 3H), 2.36−2.25 (m, 2H), 2.13 (s, 1H), 2.00−1.93 (m, 1H), 1.72−1.62 (m, 5H), 1.56−1.24 (m, 5H); ^{13}C NMR (pyridine-d_5, 100 MHz) δ 140.7, 125.9, 105.5, 83.3, 77.1, 64.9, 51.5, 43.1, 36.0, 31.4, 29.6, 24.9, 24.8, 20.2; IR (neat) 3479, 2934, 1097, cm^{-1}; HRMS ($M^+ - H$) m/z calcd for $C_{15}H_{23}O_4$ 267.1596, found 267.1594.

(5*R)-4-Hydroxy-6-methylenetricyclo[5.3.1.$0^{1,5}$]undecan-10-one (1).** A solution of *endo*-alcohol **2a** (82.0 mg, 0.306 mmol) in acetone (7.7 mL, 0.04 M) and *p*-TsOH·H_2O (70 mg, 0.367 mmol) was refluxed for 11 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, and the acetone was removed in vacuo. The mixture was extracted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 7:1) to afford a mixture of tricyclic ketone **1a** (37.3 mg, 64%) and its epimeric alcohol **1b** (5.1 mg, 8%). **Tricyclic ketone 1a:** ^1H NMR ($CDCl_3$, 300 MHz) δ 5.17 (d, J = 1.0 Hz, 1H), 5.14 (dd, J = 1.5, 1.0 Hz, 1H), 4.09 (dd, J = 13.9, 6.6 Hz, 1H), 2.97−2.95 (m, 1H), 2.62−2.51 (m, 2H), 2.43−2.37 (m, 2H), 2.17−2.06 (m, 1H), 1.92−1.56 (m, 5H), 1.32 (ddd, J = 13.7, 7.6, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.0, 155.3, 107.2, 79.1, 63.9, 60.9, 45.1, 42.9, 35.7, 35.5, 33.0, 24.5; IR (neat) 3414, 2936, 1708, 1066 cm^{-1}; HRMS (M^+) m/z calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1150. **Epimeric alcohol 1b:** ^1H NMR ($CDCl_3$, 300 MHz) δ 5.39 (d, J = 2.4 Hz, 1H), 5.02 (d, J = 1.2 Hz, 1H), 4.29 (br t, J = 4.6 Hz, 1H), 3.01 (dd, J = 7.3, 3.4 Hz, 1H), 2.88 (br s, 1H), 2.59 (ddd, 13.3, 9.8, 2.5 Hz, 1H), 2.44−2.36 (m, 2H), 2.23 (ddd, J = 11.9, 4.9, 2.5 Hz, 1H), 2.12−2.02 (m, 1H), 1.96−1.80 (m, 4H), 1.71 (d, J = 11.9 Hz, 1H), 1.57 (ddd, J = 13.4, 10.0, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.8, 153.3, 108.7, 74.3, 65.3, 60.3, 46.5, 44.4, 35.6, 35.4, 32.9, 26.0; IR (neat) 3422, 2933, 1706, 1029 cm^{-1}; HRMS (M^+) m/z calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1151.

2-[3-(1,3-Dioxolane-2-yl)propyl]-4-methoxy-6-methylbicyclo[2.2.2]oct-5-en-2-ol (31). A solution of ketone **6** (77.8 mg, 0.47 mmol) in dry THF (2 mL, 0.23 M) was slowly added dropwise onto magnesium turnings (45 mg, 1.85 mmol). To the mixture was added 2-(3-bromopropyl)-1,3-dioxolane (416 mg, 1.99 mmol), followed by a catalytic amount of 1,2-dibromoethane. After 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 9:1) to afford *endo*-**31a** (73.9 mg, 56%) and *exo*-alcohol **31b** (33.2 mg, 25%). ***endo*-Alcohol 31a:** ^1H NMR (pyridine-d_5, 300 MHz) δ 5.98 (s, 1H), 4.94 (br t, J = 4.5 Hz, 1H), 3.90−3.85 (m, 2H), 3.74−3.67 (m, 2H), 3.40 (s, 3H), 2.45 (dt, J = 10.7, 3.2 Hz, 1H), 2.29−2.15 (m, 2H), 2.10−1.90 (m, 1H), 1.88−1.72 (m, 10H), 1.58−1.30 (m, 3H); ^{13}C NMR (pyridine-d_5, 100 MHz) δ 141.7, 126.3, 105.0, 83.8, 78.3, 64.9, 51.3, 40.9, 38.8, 36.5, 35.3, 24.9, 23.2, 20.1, 17.9; IR (neat) 3500, 2936, 1095 cm^{-1}; HRMS ($M^+ - H$) m/z calcd for $C_{16}H_{25}O_4$ 281.1753, found 281.1753. ***exo*-Alcohol 31b:** ^1H NMR (pyridine-d_5, 300 MHz) δ 6.13 (s, 1H), 5.01−4.98 (m, 1H), 3.96−3.85 (m, 2H), 3.81−3.59 (m, 2H), 3.44 (s, 3H), 2.28−2.13 (m, 3H), 1.93−1.30 (m, 14H); ^{13}C NMR (pyridine-d_5, 100 MHz) δ 140.7, 126.0, 105.0, 83.5, 77.6, 64.9, 51.6, 43.1, 37.0, 36.1, 35.3, 25.0, 24.8, 20.3, 19.5; IR (neat) 3500, 2952, 1096 cm^{-1}; HRMS ($M^+ - H$) m/z calcd for $C_{16}H_{25}O_4$ 281.1753, found 281.1753.

(6*R)-5-Hydroxy-7-methylenetricyclo[6.3.1.$0^{1,6}$]dodecan-11-one (32).** A solution of *endo*-alcohol **31a** (29.8 mg, 0.105

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mmol) and *p*-TsOH·H_2O (24.1 mg, 0.127 mmol) in acetone (2.5 mL, 0.042 M) was refluxed for 11 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution, and the acetone was removed in vacuo. The mixture was extracted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 10:1) to afford six-membered tricylclic ketone **32a** (13.6 mg, 63%) and its epimeric alcohol **32b** (1.9 mg, 8%). **Tricylclic ketone 32a:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.27 (s, 1H), 5.13 (s, 1H), 3.47−3.35 (m, 1H), 2.96 (br s, 1H), 2.51−1.70 (m, 10H), 1.56−1.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.7, 156.4, 107.7, 71.7, 57.5, 54.6, 40.8, 38.2, 35.5, 34.0, 33.2, 25.8, 19.5; IR (neat) 3442, 2934, 1703, 1047 cm^{-1}; HRMS (M^+) *m*/*z* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1308. **Epimeric alcohol 32b:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.39 (s, 1H), 5.13 (s, 1H), 4.09 (br s, 1H), 2.94 (br s, 1H), 2.61−2.13 (m, 4H), 2.13 (t, J = 2.0 Hz, 1H), 2.08−1.26 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.7, 156.4, 107.7, 71.7, 57.5, 54.7, 40.8, 38.2, 35.5, 34.0, 33.2, 25.8, 19.6; IR (neat) 3444, 2933, 1699, 1092 cm^{-1}; HRMS (M^+) *m*/*z* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1307.

(3*S)-3-Butyl-4-methoxy-6-methylbicyclo[2.2.2]oct-5-en-2-one (7).** To a solution of ketone **6** (563.0 mg, 3.39 mmol) and HMPA (5 mL) in dry THF (6 mL) was added LHMDS (1.0 M in THF, 7 mL) at −78 °C. The mixture was stirred at the same temperature for 2 h, and *n*-butyl iodide (2 mL, 16.2 mmol) in THF (1 mL) was added to the reaction mixture. The reaction mixture was stirred at −20 °C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 30:1) to afford *exo* product **7** (568.0 mg, 75%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (s, 1H), 3.50 (s, 3H), 2.66 (br s, 1H), 1.97−1.63 (m, 9H), 1.50−1.20 (m, 4H), 1.16−1.04 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.8, 144.5, 120.5, 84.1, 52.9, 49.4, 40.2, 30.5, 30.0, 27.0, 24.5, 22.4, 21.5, 13.8; IR (neat) 2934, 1730, 1378, 1086 cm^{-1}; HRMS (M^+) *m*/*z* calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1620.

(3*R)-3-Butyl-4-methoxy-6-methylbicyclo[2.2.2]oct-5-en-2-one (8).** A solution of *exo* isomer **7** (568.0 mg, 2.55 mmol) in 10% methanolic NaOH (30 mL, 0.075 M) was stirred at room temperature for 3.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the excess methanol was removed in vacuo. The solution was extracted with EtOAc, washed with water and brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 80:1) to afford *exo* **7** (415.0 mg, 73%) and *endo* alcohol **8** (153.0 mg, 27%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.84 (s, 1H), 3.50 (s, 3H), 2.54 (ddd, J = 5.1, 2.6, 2.6 Hz, 1H), 1.99−1.63 (m, 9H), 1.55−1.11 (m, 5H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.3, 146.7, 121.6, 84.4, 53.0, 47.2, 39.4, 29.6, 29.2, 27.5, 22.5, 20.4, 19.6, 13.9; IR (neat) 2934, 1730, 1378, 1083 cm^{-1}; HRMS (M^+) *m*/*z* calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1619.

(2*R,3*S**)-3-Butyl-2-[2-(1,3-dioxolane-2-yl)ethyl]-4-methoxy-6-ethylbicyclo[2.2.2]oct-5-en-2-ol (9).** A solution of pure ketone **8** (182.0 mg, 0.82 mmol) in dry THF (7 mL, 0.12 M) was slowly added dropwise to magnesium turnings (70 mg, 2.88 mmol). To the mixture was added 2-(2-bromoethyl)-1,3-dioxolane (0.44 mL, 3.7 mmol) and a catalytic amount of 1,2-dibromoethane. After 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 7:1) to afford *endo* alcohol **9** (244.0 mg, 92%): ^{1}H NMR (pyridine-d_5, 300 MHz) δ 5.97 (s, 1H), 4.96 (t, J = 4.9 Hz, 1H), 4.81 (s, 1H), 3.90−3.86 (m, 2H), 3.75−3.71 (m, 2H), 3.34 (s, 3H), 2.41−2.20 (m, 4H), 2.02−1.22 (m, 15H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 142.6, 126.0, 105.8, 84.0, 77.1, 64.9, 51.2, 45.3, 38.6, 35.1, 30.8, 28.5, 28.2, 23.5, 22.8, 20.1, 19.0, 14.4; IR (neat) 3469, 2937, 1457, 1096, 1036, cm^{-1}; HRMS (M^+ − H) *m*/*z* calcd for $C_{19}H_{31}O_4$ 323.2222, found 323.2223.

(5*R,11*R**)-11-Butyl-4-hydroxy-6-ethylenetricyclo-[5.3.1.0^{1,5}]undecan-10-one (10).** A solution of alcohol **9** (161.0 mg, 0.496 mmol) and *p*-TsOH·H_2O (112 mg, 0.59 mmol) in acetone (12.3 mL, 0.038 M) was refluxed for 11 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the acetone was removed in vacuo. The solution was extracted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 8:1) to afford tricyclic ketone **10a** (89.5 mg, 73%) and its epimeric alcohol **10b** (11.0 mg, 9%). **Tricyclic ketone 10a:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.17 (dd, J = 2.0, 1.0 Hz, 1H), 5.15 (dd, J = 1.5, 1.0 Hz, 1H), 4.09 (dd, J = 14.6, 6.6 Hz, 1H), 2.85 (br d, J = 3.2 Hz, 1H), 2.66 (d, J = 6.8 Hz, 1H), 2.49 (ddd, J = 13.9, 9.4, 4.5 Hz, 1H), 2.42−2.25 (m, 2H), 2.15−1.90 (m, 3H), 1.80−1.60 (m, 4H), 1.33−0.95 (m, 6H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.1, 156.6, 108.4, 80.6, 68.1, 62.7, 52.9, 47.8, 37.1, 36.7, 31.6, 28.0, 26.8, 24.5, 24.2, 15.4; IR (neat) 3650, 2955, 2929, 1709, 1068 cm^{-1}; HRMS (M^+) *m*/*z* calcd for $C_{16}H_{24}O_2$ 248.1776, found 248.1776. **Epimeric alcohol 10b:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.39 (d, J = 2.4 Hz, 1H), 4.98 (d, J = 2.0 Hz, 1H), 4.28 (t, J = 4.4 Hz, 1H), 2.95−2.87 (m, 2H), 2.59−2.15 (m, 4H), 2.10−1.70 (m, 5H), 1.60−1.47 (m, 1H), 1.39−0.95 (m, 6H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.5, 153.2, 108.6, 73.9, 68.3, 60.9, 52.6, 47.6, 35.6, 35.1, 30.2, 26.4, 26.1, 25.0, 22.8, 13.9; IR (neat) 3647, 2925, 1699, 1541, 1457 cm^{-1}; HRMS (M^+) *m*/*z* calcd for $C_{16}H_{24}O_2$ 248.1776, found 248.1776.

(4*R,5*R**,11*R**)-11-Butyl-4-hydroxytricyclo[5.3.1.0^{1,5}]-undecan-10-one (12).** To a solution of tricyclic ketone **10a** (129.0 mg, 0.52 mmol) in ethylene glycol (1 mL) was added hydrazine hydrate (0.45 mL, 14.4 mmol) and KOH (364 mg, 6.5 mmol). The reaction mixture was stirred at 110 °C for 2 h. Following the Huang−Minlon modification, water was distilled off (180 °C oil bath), and then 2-methylenepropane-1,3-diol (0.43 mL, 5.27 mmol) was added. The reaction mixture was refluxed at 190 °C for 8 h. After cooling, the mixture was diluted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo, and the residue was chromatographed (hexane/EtOAc = 8:1) to yield tricyclic alcohol **11**. A solution of the resulting olefin **11** in EtOAc (2.5 mL) was cooled to −78 °C and exposed to ozone gas until no starting material was detected by TLC. The reaction solution was purged with dry nitrogen, and PPh_3 (251 mg) was added at −78 °C. The resulting mixture was gradually warmed to room temperature and stirred overnight. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 3:1) to afford the desired hydroxy ketone **12** (72.5 mg, 51% from **10a**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.35 (dd, J = 12.7, 6.3 Hz, 1H), 2.41 (br d, J = 3.4 Hz, 1H), 2.33 (d, J = 6.1 Hz, 1H), 2.24−2.13 (m, 1H), 1.94−1.14 (m, 16H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 222.1, 74.9, 67.7, 51.6, 51.3, 45.3, 35.2, 32.1, 30.4, 30.1, 23.5, 23.0, 20.9, 19.9, 14.0; IR (neat) 3401, 2930, 1734 cm^{-1}; HRMS (M^+) *m*/*z* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1779.

(4*R,5*R**,12*S**)-12-Butyl-4-hydroxy-7-oxatricyclo-[6.3.1.0^{1,5}]dodecan-6-one (13).** To a solution of ketone **12** (50.8 mg, 0.212 mmol) in CH_2Cl_2 (1.5 mL, 0.14 M) was added 65% *m*-CPBA (161 mg, 0.61 mmol) and anhydrous $NaHCO_3$ (106.2 mg, 1.27 mmol). The mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with EtOAc and washed with 1 N NaOH, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (hexane/EtOAc = 7:1) to afford the desired lactone **13** (44.8 mg, 83%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.62 (dd, J = 2.9, 2.8 Hz, 1H), 4.17−4.12 (m, 1H), 3.34 (s, 1H), 2.41 (d, J = 9.2 Hz, 2H), 2.04−2.00 (m, 1H), 1.87 (br d, J = 14.3 Hz, 1H), 1.70−1.62 (m, 4H), 1.58−1.19 (m, 10H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.8, 79.3, 75.1, 57.7, 44.1, 40.7, 33.3, 32.4, 31.2, 29.9, 25.2, 23.9, 22.7, 17.0, 13.8; IR (neat) 3400, 2931, 1700, 1457 cm^{-1}; HRMS (M^+) *m*/*z* calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1722.

(12*S)-12-Butyl-7-oxatricyclo[6.3.1.0^{1,5}]dodec-4-en-6-one (14).** A mixture of alcohol **13** (24.3 mg, 0.096 mmol), *p*-toluenesulfonyl chloride (55 mg, 0.29 mmol), DMAP (35.1 mg, 0.29 mmol), and dry triethylamine (0.11 mL, 0.79 mmol) in CH_2Cl_2 was refluxed for 3.5 h. The reaction mixture was diluted with 50% EtOAc in hexane. The resulting white precipitate was removed by filtration through a short column of Celite. The filtrate was concentrated in vacuo, and the residue was purified by silica gel chromatography to afford α,β-unsaturated-δ-lactone **14** (20.7 mg, 92%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (dd, *J* = 3.4, 2.2 Hz, 1H), 4.66 (dd, *J* = 5.7, 3.3 Hz, 1H), 2.60−2.30 (m, 2H), 1.88−1.26 (m, 15H), 0.92 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 144.0, 139.2, 79.7, 47.6, 44.9, 38.4, 29.9, 29.5, 28.7, 26.5, 24.9, 22.8, 17.5, 13.9; IR (neat) 2928, 1715, 1634, 1154 cm^{-1}; HRMS (M$^+$) *m*/*z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1616.

(5*S,12*S**)-12-Butyl-7-oxatricyclo[6.3.1.0^{1,5}]dodecan-6-one (17).** To a solution of α,β-unsaturated-δ-lactone **14** (28.4 mg, 0.12 mmol) in EtOH (1 mL, 0.12 M) was added 10% Pd−C (10 mg). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 1.5 h and filtered through a Celite pad. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 15:1) to afford saturated lactone **17** (27.9 mg, 97%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.59 (dd, *J* = 5.9, 3.2 Hz, 1H), 2.60 (dd, *J* = 10.5, 8.8 Hz, 1H), 2.33−2.27 (m, 1H), 1.88−1.82 (m, 1H), 1.79−1.52 (m, 9H), 1.50−1.47 (m, 1H), 1.40−1.25 (m, 6H), 1.23−1.86 (m, 1H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.4, 78.6, 51.3, 42.6, 40.8, 37.9, 32.1, 31.1, 30.1, 25.6, 24.4, 23.2, 22.9, 17.6, 13.9; IR (neat) 2945, 1729, 1134 cm^{-1}; HRMS (M$^+$) *m*/*z* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1776.

(1*R,6*S**,7*S**)-6-Butyl-1-(hydroxymethyl)spiro[4.5]-dodecane-1,7-diol (30).** To a cooled solution (−78 °C) of lactone **17** (28.0 mg, 0.12 mmol) in THF (1 mL, 0.12 M) was added KHMDS (0.5 M solution in THF, 0.56 mL). After 1.5 h, 2-(phenylsulfonyl)-3-phenyl-oxaziridine (55 mg, 0.21 mmol) in THF was added. The mixture was stirred for 1 h and quenched with saturated aqueous NH_4Cl solution and DMSO (0.4 mL). After 30 min, the mixture was extracted with EtOAc and washed with 2 N HCl solution, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 7:1) to afford crude product **29**. To a suspension of $LiAlH_4$ (9.8 mg, 0.26 mmol) in dry THF (0.5 mL) was added dropwise a solution of crude lactone **29** in dry THF (0.5 mL) at 0 °C. The resulting suspension was stirred at room temperature for 2.5 h. The reaction mixture was quenched with water (0.01 mL), 3 N NaOH (0.01 mL), and water (0.03 mL) at 0 °C. The mixture was stirred at room temperature overnight. The resulting white gel was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 1.3:1) to afford the corresponding triol **30** (22.9 mg, 72% from **17**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.88 (d, *J* = 10.7 Hz, 1H), 3.69−3.59 (m, 1H), 3.52 (d, *J* = 10.7 Hz, 1H), 2.54 (br s, 2H), 1.94−1.17 (m, 20H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 85.3, 73.4, 66.7, 50.3, 46.1, 37.1, 33.7, 33.3, 32.5, 31.6, 30.4, 23.4, 20.1, 19.0, 14.1; IR (neat) 3359, 2930 cm^{-1}; HRMS (M$^+$ − H_2O) *m*/*z* calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1943.

(6*S,7*S**)-6-Butyl-7-hydroxyspiro[4.5]decan-1-one (4).** A mixture of triol **30** (21.6 mg, 0.084 mmol) and sodium metaperiodate (36 mg, 0.17 mmol) in acetone/H_2O (1:1) was stirred at room temperature for 1 h, and the solvent was removed in vacuo. The mixture was diluted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 4:1) to afford the desired keto alcohol **4** in 96% yield (18.2 mg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.37 (br s, 1H), 2.40−2.35 (m, 1H), 2.18−2.11 (m, 1H), 1.97−1.75 (m, 6H), 1.70−1.55 (m, 2H), 1.50−1.30 (m, 5H), 1.26−1.20 (m, 4H), 1.04−0.98 (m, 1H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 223.3, 73.3, 54.7, 47.7, 38.3, 35.0, 32.7, 32.0, 30.8, 29.1, 23.3, 20.2, 19.0, 14.0; IR (neat) 3436, 2930, 1743 cm^{-1}; HRMS (M$^+$) *m*/*z* calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1777.

(11*R)-11-Butyltricyclo[5.3.1.0^{1,5}]undec-4-en-6-one (15).** A solution of alcohol **12** (24.3 mg, 0.102 mmol), *p*-toluenesulfonyl chloride (49 mg, 0.26 mmol), DMAP (41.5 mg, 0.34 mmol), and dry triethylamine (0.15 mL, 1.07 mmol) in CH_2Cl_2 was refluxed for 5 h. DBU (0.1 mL, 0.67 mmol) was then added to the reaction mixture, which was refluxed for an additional 2 h and diluted with 50% EtOAc in hexane. The resulting white precipitate was removed by filtration through a short column of Celite. The filtrate was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 12:1) to afford α,β-unsaturated ketone **15** (21.6 mg, 96%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.38 (dd, *J* = 4.5, 2.7 Hz, 1H), 2.95−2.80 (m, 1H), 2.70−2.59 (m, 1H), 2.54−2.53 (m, 1H), 1.90−1.75 (m, 6H),1.70−1.49 (m, 4H), 1.40−1.10 (m, 5H), 0.92 (t, *J* = 9.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.9, 153.8, 130.4, 55.9, 55.1, 49.2, 37.5, 36.0, 29.8, 27.8, 25.4, 23.1, 22.3, 19.4, 14.1; IR (neat) 2929, 1732 cm^{-1}; HRMS (M$^+$) *m*/*z* calcd for $C_{15}H_{22}O$ 218.1671, found 218.1677.

(5*S,11*R**)-11-Butyltricyclo[5.3.1.0^{1,5}]undecan-6-one (16).** To a solution of α,β-unsaturated ketone **15** (20.1 mg, 0.091 mmol) in EtOH (1 mL, 0.09 M) was added 10% Pd−C (10 mg). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 1.5 h and filtered through a Celite pad. The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane/EtOAc = 10:1) to afford ketone **16** (19.7 mg, 97%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.40−2.35 (m, 2H), 2.04−2.01 (m, 1H), 1.96−1.89 (m, 1H), 1.86−1.78 (m, 1H), 1.77−1.66 (m, 6H), 1.62−1.44 (m, 2H), 1.41−1.16 (m, 8H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 223.3, 58.7, 52.6, 51.2, 43.4, 35.2, 30.5, 29.8, 27.3, 25.2, 23.4, 23.1, 21.1, 20.1, 14.1; IR (neat) 2933, 1739 cm^{-1}; HRMS (M$^+$) *m*/*z* calcd for $C_{15}H_{24}O$ 220.1827, found 220.1828.

(5*S,12*R**)-12-Butyl-7-oxatricyclo[6.3.1.0^{1,5}]dodecan-6-one (17) and (5*S**,12*S**)-12-Butyl-6-oxatricyclo[6.3.1.0^{1,5}]-dodecan-7-one (17′).** A mixture of ketone **16** (19.1 mg, 0.086 mmol), 65% *m*-CPBA (68 mg, 0.26 mmol), and $NaHCO_3$ (43 mg, 0.51 mmol) in dry CH_2Cl_2 (1 mL, 0.086 M) was stirred at room temperature for 1.5 h. The reaction mixture was diluted with EtOAc and washed with 1 N NaOH, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 15:1) to afford the desired lactone **17** (13.4 mg, 66%) and its regioisomeric lactone **17′** (2.7 mg, 13%). **Regioisomeric lactone 17′:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.38 (dd, *J* = 9.0, 7.5 Hz, 1H), 2.70 (dd, *J* = 6.7, 3.3 Hz, 1H), 2.29−2.22 (m, 1H), 1.80−1.63 (m, 8H), 1.54−1.46 (m, 3H), 1.40−1.14 (m, 7H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.3, 88.5, 41.0, 39.0, 37.0, 36.5, 33.2, 32.5, 29.6, 24.3, 22.8, 22.1, 20.0, 20.0, 14.0; IR (neat) 2934, 1738, 1101 cm^{-1}; HRMS (M$^+$) *m*/*z* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1780.

(4*R,5*R**,11*R**)-11-Butyl-4-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}tricyclo[5.3.1.0^{1,5}]undecan-6-one (25).** To a stirred solution of alcohol **12** (22.5 mg, 0.09 mmol) in dry CH_2Cl_2 (1 mL, 0.09 M) was added DMAP (5 mg, 0.04 mmol), imidazole (20 mg, 0.29 mmol) and TBDMSCl (27 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 8 h before it was poured into brine and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 15:1) to afford silyl ether **25** (29.3 mg, 90%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.30−4.24 (m, 1H), 2.34 (d, *J* = 4.9 Hz, 2H), 2.15−2.03 (m, 1H), 1.88 (dt, *J* = 12.3, 5.7 Hz, 1H), 1.77−1.10 (m, 15H), 0.93−0.83 (m, 12H), 0.13−0.05 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.1, 75.5, 68.4, 51.6, 51.2, 44.4, 36.3, 32.3, 30.5, 30.1, 25.8, 25.7, 23.5, 23.1, 21.1, 20.0, 18.1, 14.0, −3.6, −4.7, −4.8; IR (neat) 2929, 1734, 1058 cm^{-1}; HRMS (M$^+$ − CH_3) *m*/*z* calcd for $C_{21}H_{38}O_2Si$ 335.2406, found 335.2407.

(4*R,5*R**,12*S**)-12-Butyl-4-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-7-oxatricyclo[6.3.1.0^{1,5}]-dodecan-6-one (26).** A mixture of ketone **25** (28.1 mg, 0.08 mmol), 65% *m*-CPBA (60

mg, 0.23 mmol) and anhydrous $NaHCO_3$ (38 mg, 0.46 mmol) in dry CH_2Cl_2 (1 mL, 0.08 M) was stirred for 1.5 h at room temperature. The reaction mixture was diluted with EtOAc and washed with 1 N NaOH, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 20:1) to afford the desired lactone **26** (24.2 mg, 82%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.55 (dd, J = 5.4, 3.2 Hz, 1H), 4.33 (dd, J = 5.9, 1.5 Hz, 1H), 2.56 (d, J = 5.9 Hz, 1H), 1.93−1.23 (m, 17H), 0.93−0.85 (m, 12H), 0.14−0.07 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 93.5, 78.3, 60.1, 42.8, 41.0, 39.1, 33.7, 30.1, 29.6, 25.8, 24.5, 24.2, 22.9, 22.0, 19.8, 18.1, 14.0, −4.6, −4.9, −5.0; IR (neat) 2930, 1734, 1073 cm^{-1}; HRMS ($M^+ - CH_3$) m/z calcd for $C_{21}H_{38}O_3Si$ 331.2355, found 331.2357.

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for **1**, **2**, **4**, **7**−**10**, **12**−**17**, **17′**, **25**, **26** and **30**−**32**, the IR and HRMS spectra for **4,** and the NOE spectra for **10a** and **10b**. This material is available free of charge via the Internet at http://pubs.acs.org..

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