JOC The Journal of Organic Chemistry

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Intramolecular Cycloaddition Reactions of *cis*-1,2-Dihydrocatechol Derivatives Incorporating C3-Tethered Diazoketones, Nitrile Oxides, and Azides: Stereocontrolled Routes to Enantiomerically Pure Spiro[5.5]undecanes and Related Systems

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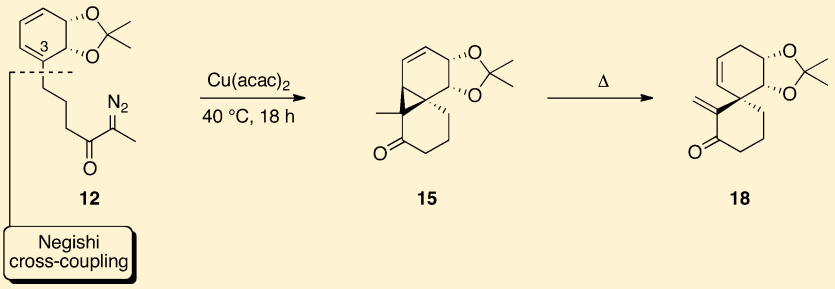
Supporting Information

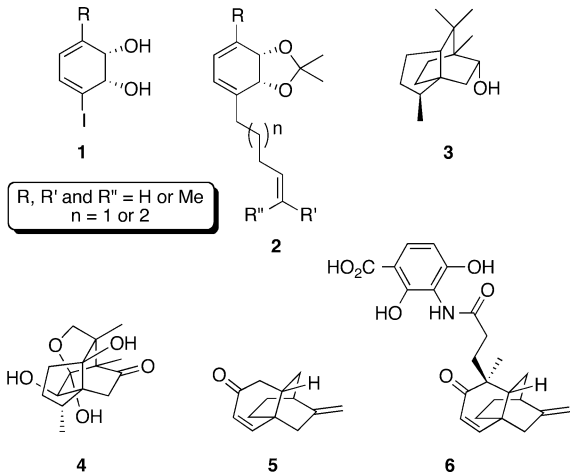


ABSTRACT: A series of enantiomerically pure *cis*-1,2-dihydrocatechol derivatives incorporating C3-tethered diazoketone, nitrile oxide, or azide residues has been prepared from the precursor iodide **7** using Negishi cross-coupling reactions. Such derivatives, including diazoketone **12**, participate in regio- and stereo-selective intramolecular cycloaddition reactions to give adducts, for example, **15**, that are readily elaborated to spiro[5.5]undecanes such as **18**.

INTRODUCTION

Recently, we demonstrated that the acetonide derivatives of the enzymatically derived and highly enantiomerically enriched *cis*-1,2-dihydrocatechols **1** (R = H or Me) can be engaged in Negishi-type cross-coupling reactions so as to generate trienes of the general form **2** and that these, in turn, participate in efficient intramolecular Diels–Alder (IMDA) reactions to form a range of synthetically useful tricyclic adducts.[1,2] In particular, we have employed such protocols in an enantioselective total synthesis of the sesquiterpenoid khusiol (**3**)[1c] and are currently seeking to extend this work so as to generate the structurally related and neurotrophically active congener 11-*O*-debenzoyltashironin (**4**).[1d] Similar chemistry has been employed in the preparation of the tricyclic enone **5**, the acquisition of which constitutes a formal total synthesis of the potent antibacterial agent platencin (**6**).[1a]

In principle, equivalent intramolecular cycloaddition reactions involving the same diene substrates but now incorporating tethered diazoketone, nitrile oxide, or azide residues could provide useful new routes to a range of natural product frameworks. Herein, therefore, we report the outcome of a study that has established methods for preparing the relevant substrates and demonstrated that these do indeed engage in stereocontrolled cycloaddition reactions to give a range of novel adducts. Details are presented in the following sections.



RESULTS AND DISCUSSION

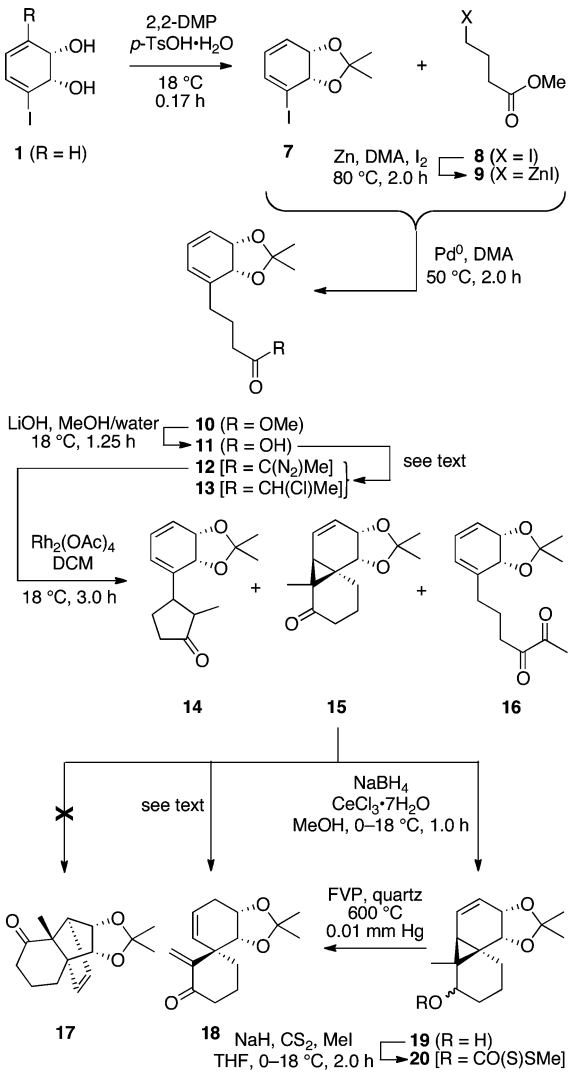
Chemistry of Diazoketone-Containing Systems. Initial studies were focused on preparing α-diazoketones tethered to the *cis*-1,2-dihydrocatechol core and able, under appropriate conditions, to engage in intramolecular cycloaddition reactions to deliver alkenylcyclopropanes that might themselves undergo ring-expansion reactions to give novel cyclopentenes.[3] The

Received: May 2, 2013
Published: May 29, 2013

dx.doi.org/10.1021/jo400952u | J. Org. Chem. 2013, 78, 7100–7111

synthesis of a substrate used to test such possibilities is shown in Scheme 1 and starts with the conversion of the enantiomerically pure diol **1** (R = H)[4] into the previously reported[5] acetonide **7** (88%) under established conditions. Conversion of methyl 4-iodobutanoate (**8**)[6] into the corresponding organozinc species (**9**) was readily achieved by treating the former compound with zinc powder in the presence of catalytic quantities of molecular iodine and using *N*,*N*-dimethylacetamide (DMA) as solvent.[7] Compound **9** so-formed readily engaged in a Negishi cross-coupling reaction with iodide **7** using $(Ph_3P)_4Pd$ as catalyst to give the ester **10** in 83% yield. Saponification of the last compound using lithium hydroxide in aqueous methanol afforded, after acidic workup, the corresponding carboxylic acid **11** (96%). Various protocols were examined so as to convert compound **11** into the diazoketone **12**. For example, reaction of acid **11** with ethyl chloroformate in the presence of triethylamine followed by treatment of the resulting mixed anhydride with diazoethane[8] gave the required diazoketone **12** (22%), but the major product of the reaction was the chromatographically separable ethyl ester of acid **11** (58%). Treatment of acid **11** with 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine[9] and reaction of the ensuing acid chloride with diazoethane also gave the target compound **12** (15%), but now, the major product was the α-chloroketone **13** (62%), which was obtained as a 1:1 mixture of diastereoisomers. Through a minor modification of this second process, involving the addition of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) after acid chloride formation but before addition of the diazoethane, compound **12** could be obtained in 83% yield.

Scheme 1



With compound **12** in hand, its behavior in the presence of either dirhodium tetraacetate or copper(II) acetylacetonate was explored.[10] When the former metal complex was used in dichloromethane at 18 °C, a chromatographically separable mixture of compounds **14** (10%), **15** (35%), and **16** (23%) was obtained. Product **14**, which presumably arises through a C−H insertion process, was obtained as essentially a single diasteroisomer, but the configurations at the stereogenic centers associated with the newly formed five-membered ring were not determined. The structure of cyclopropane **15**, the desired product of the reaction, was established by single-crystal X-ray analysis,[11] demonstrating that the intramolecular cyclopropanation step leading to this compound is a completely diastereoselective process involving delivery of the carbenoid to the less congested β face of the diene.[12] The α-diketone **16** presumably arises through rhodium-catalyzed oxidation of the substrate **12** by adventitious oxygen,[13] a process that could not be completely suppressed despite strenuous efforts to operate under strictly anaerobic conditions. A much more satisfactory outcome was observed when compound **12** was treated with copper(II) acetylacetonate in refluxing dichloromethane and, under such conditions, the desired cyclopropane **15** was now obtained in 85% yield.

With compound **15** available in significant quantity by the pathway defined above, studies were undertaken to establish if this would engage in an alkenylcyclopropane to cyclopentene rearrangement reaction thereby generating tetracyclic acetonide **17**. The latter compound embodies the carbotricyclic core associated with the myltaylane-type class of sesquiterpenoids, members of which have been isolated from various sources including liverworts and certain of which display interesting biological properties.[14] In initial attempts to effect the desired rearrangement, a toluene solution of cyclopropane **15** was treated with one molar equivalent of $Rh(CO)_2(acac)$[15] and then heated at 140 °C, but the only isolable product of reaction was compound **18** (55%) that presumably arises through the operation of a 1,5-hydride shift.[16] The same transformation proceeded in 70% yield when the substrate was simply heated at 140 °C suggesting that $Rh(CO)_2(acac)$ played little, if any, role in the original conversion. All the spectral data obtained on compound **18** were in complete accord with the assigned structure. In particular, the ^{1}H NMR spectrum of this enone displayed two mutually coupled (J = 1.8 Hz) one-proton doublets at 5.72 and 5.13 that are assigned to the geminally related protons of the exocyclic C−C double bond.

Several studies on the flash vacuum pyrolytic (FVP)-promoted rearrangement of alkenylcyclopropanes[3] suggest that isomerism to the corresponding cyclopentene takes place at approximately 600 °C while lower temperatures favor a 1,5-hydride shift.[16] Furthermore, it has been shown that, in certain cases, the product of a 1,5-hydride shift can be converted into the corresponding cyclopentene at elevated temperatures.[16] In addition, it has been noted that the alkenylcyclopropane to cyclopentene rearrangement reaction can be promoted by washing the pyrolysis tube with a lead(II) carbonate slurry prior to use. The origins of this effect are attributed to the capacity of lead to stabilize radical intermediates.[16] On this basis, the

dx.doi.org/10.1021/jo400952u | J. Org. Chem. 2013, 78, 7100−7111

behavior of compound **15** under FVP conditions was examined. In the event, the only product obtained on subjecting this substrate to FVP at 600 °C was the previously observed spiro[5.5]undecane **18** that was obtained in 98% yield. Heating the substrate under the same conditions at 700 and 750 °C provided product **18** in 75% and 36% yields, respectively, while at 800 °C, complete decomposition was observed. No evidence was obtained for the formation of isomer **17** under any of the conditions examined.

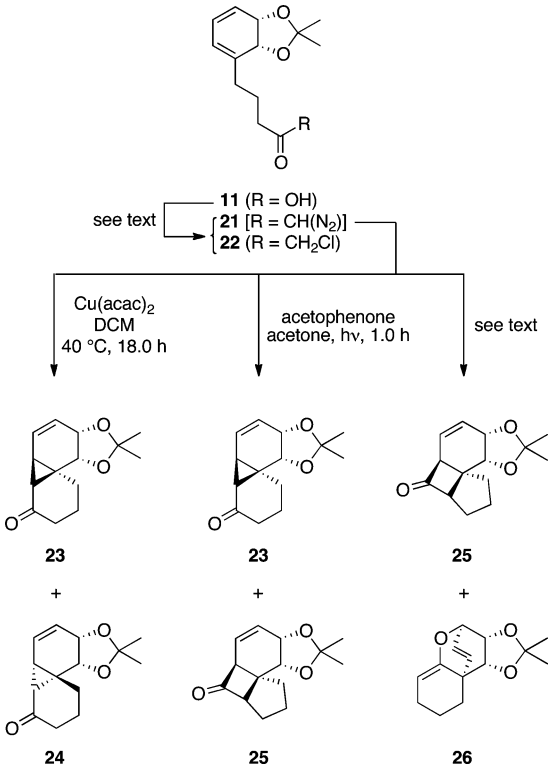
On the basis that the ketone carbonyl residue associated with compound **15** may be having an influence on the rearrangement pathway it follows,[17] it was reduced to the corresponding pair of epimeric alcohols **19** under Luche conditions (using $NaBH_4$ and $CeCl_3{\cdot}7H_2O$),[18] but when the latter material (obtained as a 2:1 mixture) was subjected to FVP at 600 °C, then the enone **18** (75%) was again observed. Presumably this conversion involves reoxidation (by an unknown mechanism) of alcohol **19** to the precursor **15** that then rearranges as seen previously. In an effort to generate a completely deoxygenated system, alcohol **19** was first converted into the corresponding *S*-methyl xanthate **20** (74%) but upon exposure of the latter to tri-*n*-butyltin hydride only a complex product mixture was obtained, probably as a result of the generation of a cyclopropylmethyl radical that is likely to engage in a range of ring-cleavage processes.[19]

In light of the ready participation of compound **15** in a 1,5-hydride shift (thereby generating enone **18**), the desmethyl analogue was sought as this cannot engage in the same type of process. The reaction sequence leading to this analogue is shown in Scheme 2 and starts with the conversion of the acid **11** into the corresponding diazoketone **21** (92%) under the optimized conditions used earlier for the formation of congener **12**. When this conversion was carried out in the absence of DMAP, then a chromatographically separable mixture of compound **21** (71%) and the α-chloromethylketone **22** (18%) was obtained. Upon exposure to 10 mol % $Cu(acac)_2$ in dichloromethane at 40 °C, diazoketone **21** engaged in the anticipated cyclization process with a chromatographically separable mixture of diastereoisomeric cyclopropylketones **23** (79%) and **24** (10%) being obtained. The structure of the former and predominant product, which arises through carbenoid addition to the more accessible β-face of the proximate olefin, was confirmed by a single-crystal X-ray analysis.[11] Disappointingly, all efforts to engage compound **23** in an alkenylcyclopropane to cyclopentene rearrangement reaction failed. Under FVP conditions, either recovery of starting material was observed (92% recovery at 600 °C) or, at higher temperatures, decomposition took place. In an effort to effect the desired rearrangement the substrate was independently exposed to $Rh(CO)_2(acac)$[15] and $Ni(cod)_2$ in the presence of PBu_3[20] but to no useful effect.

The photochemical behavior of diazoketone **21** was also examined, and various potentially useful outcomes were observed. In particular, photolysis at 18 °C of a solution of this compound in acetone containing acetophenone for 1 h resulted in the formation of a mixture of the previously obtained cyclopropylketone **23** (61%) and the cyclobutanone **25** (11%). The latter product presumably arises from an initial Wolff rearrangement with the resulting ketene then engaging in a β-face addition reaction to the proximate double bond. The presence of the cyclobutanone ring within compound **25** was clearly evident from the derived ^{13}C NMR spectrum that displayed a characteristic carbonyl-carbon resonance at δ 211.8. The IR spectrum showed a C═O stretching band at 1775 cm^{-1}, a value that suggests this chromophore is embedded within a four-membered ring. The intermediacy of a ketene in the conversion **21** → **25** is supported by the observation that when the reaction was carried out in the presence of methanol then the methyl ester of acid **11** (78%) was obtained. Previous reports suggest that in the presence of triplet sensitizers (such as acetophenone) the Wolff rearrangement of diazoketones is suppressed, sometimes completely, and that carbene formation is strongly favored.[21] Accordingly, and in an effort to promote the cyclobutanone forming process, a solution of substrate **21** in 1:70 v/v 1,4-dioxane/hexane was irradiated (at 18 °C) for 0.33 h, and the ensuing reaction mixture, now presumed to contain the derived ketene, was heated at 100 °C for 1 h and then cooled and quenched with methanol. As a result, the previously obtained cyclobutanone **25** (20%) and the dihydropyran **26** (31%), presumably arising from an intramolecular hetero Diels–Alder cycloaddition reaction, were obtained. These results suggest that ketene formation is relatively rapid and that the subsequent cycloaddition reactions of this species are slower. The illustrated stereochemistry is assigned to compound **26** on the basis that the dienophilic C═O of the ketene adds to the more accessible β face of the diene residue embodied within the *cis*-1,2-dihydrocatechol substructure.

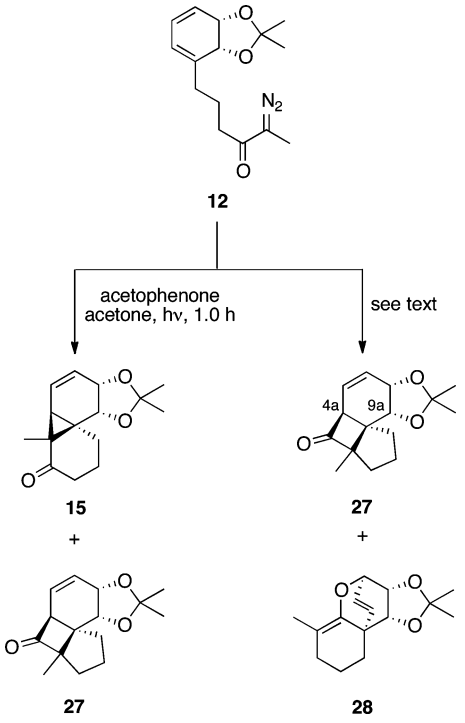
The analogous photochemical behavior of diazoketone **12** was examined, and the outcomes are presented in Scheme 3. Thus, irradiation of an acetone solution of this substrate in the presence of acetophenone at 18 °C for 1 h afforded a chromatographically separable mixture of the previously observed cyclopropane **15** (63%) and the cyclobutanone **27** (6%). In contrast, photolysis of the same substrate under nontriplet sensitized conditions afforded a chromatographically

Scheme 2

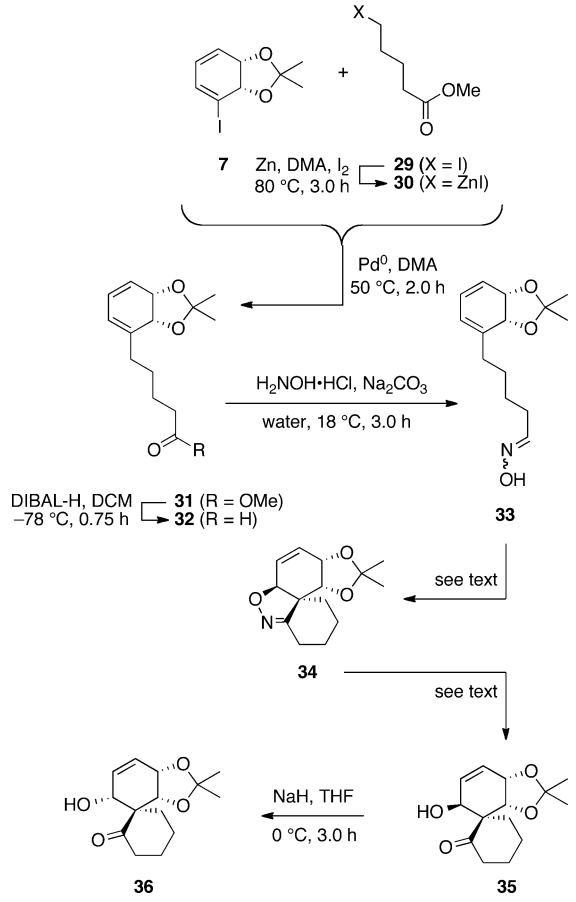


dx.doi.org/10.1021/jo400952u | J. Org. Chem. 2013, 78, 7100–7111

Scheme 3



Scheme 4



separable mixture of cyclobutanone **27** (35%) and the annulated dihydropyran **28** (35%). Once again, the assignment of stereochemistry to these products follows from the argument that the precursor carbenoid and ketene, respectively, add to the pendant *cis*-1,2-dihydrocatechol residue from the more accessible β-face of this moiety. Support for such assignments follows from certain NOE experiments. In particular, no interaction was observed between H4a and H9a in compound **27**, supporting the proposed structure.

Chemistry of Nitrile Oxide-Containing Systems. The engagement of nitrile oxide residues tethered to the *cis*-1,2-dihydrocatechol core in intramolecular cycloaddition reactions with this moiety was the next process to be examined.[22] The synthesis of the substrate required for this purpose is shown in Scheme 4. Thus, the previously reported[23] iodide **29** was converted into corresponding organozinc species **30** (using conditions defined earlier for the conversion **8** → **9**) that was itself engaged in a Negishi-type coupling with acetonide **7** to afford the methyl ester **31** (74%). This last compound was identical, in all respects, with the material obtained via reaction of the ketene derived from diazoketone **21** with methanol. DIBAL-H-mediated reduction of compound **31** afforded the corresponding aldehyde **32** (99%) that was condensed with hydroxylamine and so delivering the rather unstable oxime **33** in 85% yield and as an approximately 1:1 mixture of *E* and *Z* isomers. Treatment of this mixture with *N*-chlorosuccinimide in the presence of triethylamine[24] is presumed to have generated, via the intermediate *C*-chlorooxime, the target nitrile oxide. However, this was not isolated because it underwent spontaneous intramolecular 1,3-dipolar cycloaddition reaction to give the isoxazoline **34** (82%). The structure of this compound was established by single crystal X-ray analysis[11] revealing that the nitrile oxide residue within the precursor adds to the proximate double bond of the tethered diene moiety from the more accessible β-face. A more direct, albeit slightly lower yielding (70%) route to heterocycle **34** involved the direct oxidation of oxime **33** with (diacetoxyiodo)benzene.[25]

The N−O bond within isoxazoline **34** could be cleaved using either iron powder in the presence of aqueous ammonium chloride or stoichiometric amounts of $Mo(CO)_6$,[26] and by such means, the spiro[5.5]undecane **35** was obtained in 70% and 82% yields, respectively. Upon treating the later compound with sodium hydride it engaged in a retro-aldol/aldol sequence thereby generating a 1:1.5 mixture of substrate **35** (23%) and its chromatographically separable isomer **36** (35%). A comparison of the ^{1}H and ^{13}C NMR spectral data sets obtained on these compounds suggests they possess a high degree of "chemical homology", as would be expected for epimerically related systems.

Chemistry of Azide-Containing Systems. The intramolecular addition of a pendant azide to the *cis*-1,2-dihydrocatechol moiety was the final process to be examined as part of the present study.[27] The substrate used for this purpose was prepared by the straightforward pathway shown in Scheme 5. This started with the $LiAlH_4$-mediated reduction of the previously mentioned ester **10** to the corresponding alcohol **37** (85%) and conversion of the latter into the mesylate **38** (99%) under the conditions reported by Crossland and Servis.[28] In the final step, sulfonate ester **38** was treated with sodium azide in DMF producing the target azide **39** in 81% yield. All the spectral data acquired on this product were in complete accord with the assigned structure. Most notably, the IR spectrum of this material displayed a characteristic azide-stretching band at 2096 cm^{-1}.

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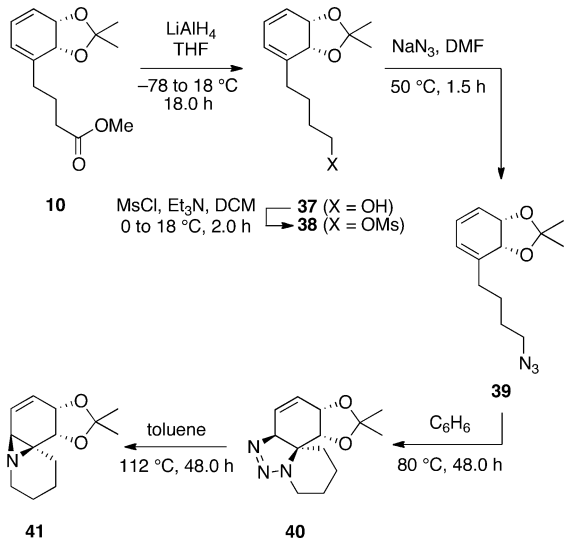
Scheme 5



Upon simply heating azide **39** in refluxing benzene, the anticipated cycloaddition reaction took place producing the crystalline triazoline **40** in 90% yield. The structure of the latter compound was confirmed by single-crystal X-ray analysis[11] establishing that, once again, the intramolecular addition process involved delivery of the azido group to the more accessible β-face of the *cis*-1,2-dihydrocatechol residue. Heating the triazoline **40** in refluxing toluene resulted in the extrusion of dinitrogen and the consequent formation of the annulated aziridine **41** (85%). A more direct route to the latter compound involved heating azide **39** in refluxing toluene for 72 h. By such means, the aziridine was now obtained in 79% yield.

CONCLUSION

The studies detailed above have revealed that *cis*-1,2-dihydrocatehols incorporating C3-tethered enophiles engage in regio- and stereo-selective cycloaddition reactions to deliver a range of structurally interesting motifs. Most notably, perhaps, enantiomerically pure spiro[5.5]undecanes can be obtained by such means and thus offering the prospect of being able to use the reported protocols in the synthesis of, inter alia, members of the chamigrane class of natural products.[29] In this connection, it is worth noting that the hetero-Diels–Alder adduct **26** should, in principle and by virtue of incorporating an enol ether residue, be capable of hydrolytic cleavage thereby leading to another functionalized spiro[5.5]undecane. Work aimed at pursuing these various possibilities is now underway. Results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, ^{1}H and ^{13}C NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a spectrometer operating at 300 or 400 MHz for proton and 75 or 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) (multiplicity, coupling constant(s) J (Hz), relative integral) where multiplicity is defined as follows: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Samples were analyzed by IR spectroscopy (ν_{max}) as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph–mass spectrometer while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Optical rotations were recorded in $CHCl_3$ at 20 °C. Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc)/water (37.5 g/7.5 g/37.5 g/720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[30] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol, and dichloromethane (DCM) were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[31] Where necessary, reactions were performed under an argon atmosphere.

Compound 7. Acetonide 7 was prepared in 88% yield from diol **1** (R = H) using previously described[5] protocols. The spectroscopic data obtained on the product 7 matched those reported previously.[5]

Compound 10. A magnetically stirred portion of zinc powder (940 mg, 14.4 mmol) maintained under nitrogen was treated with molecular iodine (122 mg, 0.48 mmol) and then, after 0.03 h, with *N,N*-dimethylacetamide (5 mL). A solution of iodide **8** (2.19 g, 9.60 mmol) in *N,N*-dimethylacetamide (5 mL) was added to the reaction mixture, and the resulting suspension was stirred at 80 °C for 3 h and then cooled to 50 °C. The mixture thus obtained was treated with a solution of $Pd(PPh_3)_4$ (664 mg, 0.58 mmol) in *N,N*-dimethylacetamide (5 mL), the ensuing solution was stirred for 0.08 h and then acetonide **7** (1.60 g, 5.75 mmol) in *N,N*-dimethylacetamide (3 mL) was added. The mixture thus obtained was stirred at 50 °C for 2 h and then treated with $NaHCO_3$ (25 mL of a saturated aqueous solution) before being filtered through diatomaceous earth; the separated aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 25 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:99 → 1:9 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions (R_f = 0.5 in 3:7 v/v ethyl acetate/hexane) afforded ester **10** (1.20 g, 83%) as a clear, colorless oil, $[\alpha]_D$ +119 (*c* 1.1, $CHCl_3$) [Found: (M + Na)$^+$, 275.1255. $C_{14}H_{20}O_4$ requires (M + Na)$^+$, 275.1259]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (dd, J = 5.7 and 9.6 Hz, 1H), 5.84 (dd, J = 3.9 and 9.6 Hz, 1H), 5.73 (d, J = 5.7 Hz, 1H), 4.66 (dd, J = 3.9 and 8.5 Hz, 1H), 4.53 (d, J = 8.5 Hz, 1H), 3.66 (s, 3H), 2.35 (t, J = 7.3 Hz, 2H), 2.25 (m, 2H), 1.85 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7 (C), 137.6 (C), 124.8 (CH), 123.1 (CH), 119.1 (CH), 105.5 (C), 73.4 (CH), 71.4 (CH), 60.5 (CH_3), 34.0 (CH_2), 33.1 (CH_2), 27.1 (CH_3), 25.3 (CH_3), 22.7 (CH_2). ν_{max} 2986, 2934, 1738, 1436, 1370, 1210, 1160, 1028, 868 cm^{-1}. Mass spectrum (EI, 70 eV) *m/z* 250 (1%), 205 (21), 194 (28) 163 (98), 162 (95), 145 (25), 134 (32), 120 (95), 107 (100), 91 (66), 77 (59), 55 (67), 43 (78).

Compound 11. A magnetically stirred solution of ester **10** (267 mg, 1.06 mmol) in methanol/water (24 mL of a 2:1 v/v mixture) containing $LiOH·H_2O$ (222 mg, 5.30 mmol) was stirred at 18 °C for 1.25 h and then concentrated under reduced pressure to a third of its original volume. Citric acid was added to the concentrate until the pH was less than 6 and then it was extracted with ethyl acetate (5 × 10 mL). The combined organic fractions were washed with brine (1 × 15 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give acid **11** (243 mg, 96%) as a white, crystalline solid, mp 33–34 °C, $[\alpha]_D$ +114 (*c* 1.3, $CHCl_3$) (R_f = 0.2 in 3:7 v/v ethyl acetate/hexane) [Found: (M + Na)$^+$, 261.1104. $C_{13}H_{18}O_4$ requires (M + Na)$^+$, 261.1103]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (dd, J = 5.7 and 9.6 Hz, 1H), 5.80 (dd, J = 3.9 and 9.6 Hz, 1H), 5.74 (d, J = 5.7 Hz, 1H), 4.67 (dd, J = 3.9 and 8.7 Hz, 1H), 4.53 (d, J =

dx.doi.org/10.1021/jo400952u | J. Org. Chem. 2013, 78, 7100–7111

8.7 Hz, 1H), 2.40 (t, J = 7.5 Hz, 2H), 2.27 (m, 2H), 1.88 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H) (signal due to carboxylic acid proton not observed). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.6 (C), 136.9 (C), 124.4 (CH), 122.8 (CH), 118.9 (CH), 105.2 (C), 73.0 (CH), 71.1 (CH), 33.4 (CH_2), 32.7 (CH_2), 26.7 (CH_3), 24.9 (CH_3), 22.0 (CH_2). ν_{max} 3220, 3046, 2985, 2934, 1707, 1406, 1371, 1237, 1209, 1157, 1042 cm^{-1}; Mass spectrum (ESI) 261 [$(M + Na)^+$, 30%], 203 (27), 184 (51) 163 (94), 145 (23), 107 (100).

Compounds 12 and 13. Method A: A magnetically stirred solution of acid **11** (359 mg, 1.50 mmol) in dichloromethane (20 mL) was treated with ethyl chloroformate (359 μL, 3.75 mmol) and then triethylamine (312 μL, 2.25 mmol). The resulting solution was stirred at approximately 18 °C for 0.5 h before being quenched with brine (20 mL). The separated organic phase was cooled to 0 °C and then treated with an excess of ethereal diazoethane prepared by the method of de Boer and Backer.[8] The ensuing mixture was warmed to 18 °C, stirred at this temperature for 18 h and then concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 3/7 v/v ethyl acetate/hexane) afforded the ethyl ester of acid **11** (232 mg, 58%) as a clear, colorless oil, $[\alpha]_D$ +122 (c 1.1, $CHCl_3$) (Found: $M^{+\bullet}$, 266.1528. $C_{15}H_{22}O_4$ requires $M^{+\bullet}$, 266.1518]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.97 (dd, J = 5.7 and 9.6 Hz, 1H), 5.80 (dd, J = 3.6 and 9.6 Hz, 1H), 5.73 (d, J = 5.7 Hz, 1H), 4.66 (dd, J = 3.6 and 8.7 Hz, 1H), 4.53 (d, J = 8.7 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 2.33 (t, J = 7.5 Hz, 2H), 2.25 (m, 2H), 1.87 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7 (C), 137.6 (C), 124.8 (CH), 123.1 (CH), 119.1 (CH), 105.5 (C), 73.4 (CH), 71.4 (CH), 60.5 (CH_2), 34.1 (CH_2), 33.2 (CH_2), 27.1 (CH_3), 25.3 (CH_3), 22.7 (CH_2), 14.5 (CH_3). ν_{max} 2983, 2933, 1732, 1371, 1238, 1209, 1159, 1141, 1028, 866 cm^{-1}. Mass spectrum (EI, 70 eV) 266 ($M^{+\bullet}$, <1%), 251 (2), 236 (2), 208 (35), 163 (96), 162 (97), 145 (22), 120 (100), 107 (98), 91 (74), 77 (62), 55 (61), 43 (74).

Concentration of fraction B (R_f = 0.3 in 3:7 v/v ethyl acetate/hexane) afforded compound **12** (91 mg, 22%) as a clear, light-yellow oil, $[\alpha]_D$ +95 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.93 (dd, J = 5.7 and 9.6 Hz, 1H), 5.76 (dd, J = 3.6 and 9.6 Hz, 1H), 5.70 (d, J = 5.7 Hz, 1H), 4.63 (dd, J = 3.6 and 8.4 Hz, 1H), 4.48 (d, J = 8.4 Hz, 1H), 2.47 (t, J = 7.5 Hz, 2H), 2.23 (m, 2H), 1.91 (s, 3H), 1.85 (m, 2H), 1.36 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.3 (C), 137.2 (C), 124.3 (CH), 122.9 (CH), 118.9 (CH), 105.1 (C), 73.0 (CH), 71.2 (CH), 36.9 (CH_2), 36.5 (C), 33.0 (CH_2), 26.8 (CH_3), 24.9 (CH_3), 22.1 (CH_2), 8.0 (CH_3). ν_{max} 2984, 2930, 2068, 1634, 1458, 1377, 1261, 1208, 1158, 1087 cm^{-1}. Mass spectrum (EI, 70 eV) 217 (13%), 201 (55) 190 (20), 173 (20), 163 (53), 145 (43), 133 (37), 120 (73), 107 (100), 91 (75), 69 (55), 55 (55), 43 (87). The unstable nature of this compound prevented the acquisition of HRMS or microanalytical data.

Method B: 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine[9] (36 μL, 0.27 mmol) was added to a magnetically stirred solution of acid **11** (64 mg, 0.27 mmol) in dichloromethane (5 mL), and the resulting mixture was cooled to 0 °C. An excess of ethereal diazoethane[8] maintained at 0 °C was added to the reaction mixture that was then allowed to warm to 18 °C and stirred at this temperature for 0.25 h. The ensuing solution was concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 3/7 v/v ethyl acetate/hexane) afforded compound **13** (48 mg, 62%) as a clear, colorless oil [Found: $(M - CH_3\bullet)^+$, 269.0941. $C_{15}H_{21}{}^{35}ClO_3$ requires $(M - CH_3\bullet)^+$, 269.0944]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (dd, J = 5.7 and 9.6 Hz, 1H), 5.80 (dd, J = 3.6 and 9.6 Hz, 1H), 5.74 (d, J = 5.7 Hz, 1H), 4.67 (dd, J = 3.6 and 8.7 Hz, 1H), 4.53 (d, J = 8.7 Hz, 1H), 4.33 (q, J = 6.9 Hz, 1H), 2.37 (m, 2H), 2.26 (m, 2H), 1.84 (m, 2H), 1.59 (d, J = 6.9 Hz, 3H), 1.41 (s, 3H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.5 (C), 137.6 (C), 124.7 (CH), 123.3 (CH), 119.3 (CH), 105.5 (C), 73.4 (CH), 71.5 (CH), 58.7 (CH), 38.0 (CH_2), 33.1 (CH_2), 27.1 (CH_3), 25.3 (CH_3), 21.4 (CH_2), 20.4 (CH_3). ν_{max} 2928, 1721, 1455, 1377, 1260, 1160, 1063 cm^{-1}. Mass spectrum MS (EI, 70 eV) 271 and 269 [$(M - CH_3\bullet)^+$, 5 and 2%), 269 (5), 226 (22) 190 (22), 173 (25), 163 (87), 145 (22), 133 (35), 107 (100), 91 (84), 77 (55), 65 (36), 55 (65), 43 (89).

Concentration of fraction B (R_f = 0.3 in 3/7 v/v ethyl acetate/hexane) afforded compound **12** (11 mg, 15%) as a light-yellow oil. This material was identical, in all respects, with that obtained via Method A described above.

Method C: 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine[9] (173 μL, 1.31 mmol) was added to a magnetically stirred solution of acid **11** (313 mg, 1.31 mmol) in dichloromethane (25 mL) maintained at 18 °C. The resulting mixture was stirred at this temperature for 0.08 h, treated with 4-(*N*,*N*-dimethylamino)pyridine (320 mg, 2.62 mmol), and then, cooled to 0 °C and treated with an excess of ethereal diazoethane.[8] The resulting solution was then warmed to 18 °C and stirred at this temperature for 0.25 h before being concentrated under reduced pressure to give an oily yellow solid. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f = 0.3 in 3:7 v/v ethyl acetate/hexane), the title compound **12** (304 mg, 83%) as a clear, yellow oil. This material was identical, in all respects, with that obtained via Method A described above.

Compounds 14–16. Method A: A degassed solution of diazoketone **12** (193 mg, 0.70 mmol) in dichloromethane (70 mL) was added over 2 h to a magnetically stirred and degassed solution of $Rh_2(OAc)_4$ (15 mg, 0.04 mmol) in dichloromethane (50 mL) maintained at 18 °C. The ensuing mixture was stirred for a further 1 h at 18 °C and then concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 1:99 → 1:9 v/v ethyl acetate/hexane gradient elution) afforded three fractions, A–C.

Concentration of fraction A (R_f = 0.5 in 3:7 v/v ethyl acetate/hexane) afforded dione **16** (43 mg, 23%) as a clear, bright-yellow oil, $[\alpha]_D$ +82 (c 0.7, $CHCl_3$) (Found: $M^{+\bullet}$, 264.1364. $C_{15}H_{20}O_4$ requires $M^{+\bullet}$, 264.1362). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.97 (dd, J = 5.7 and 9.6 Hz, 1H), 5.80 (dd, J = 3.9 and 9.6 Hz, 1H), 5.72 (d, J = 5.7 Hz, 1H), 4.66 (dd, J = 3.9 and 8.7 Hz, 1H), 4.52 (d, J = 8.7 Hz, 1H), 2.78 (m, 2H), 2.33 (s, 3H), 2.22 (m, 2H), 1.85 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.3 (C), 197.7 (C), 137.5 (C), 124.8 (CH), 123.2 (CH), 119.3 (CH), 105.5 (C), 73.3 (CH), 71.4 (CH), 35.4 (CH_2), 33.1 (CH_2), 27.1 (CH_3), 25.3 (CH_3), 24.0 (CH_3), 20.9 (CH_2). ν_{max} 2984, 2928, 1713, 1456, 1378, 1369, 1258, 1236, 1211, 1159, 1025, 889 cm^{-1}. Mass spectrum (EI, 70 eV) 264 ($M^{+\bullet}$, 3%), 189 (23), 163 (86), 145 (25), 135 (25), 121 (40), 120 (44), 107 (96), 91 (53), 77 (43), 55 (43), 43 (100).

Concentration of fraction B (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane) afforded a white solid that was recrystallized (hexane/diethyl ether) to give cyclopropane **15** (61 mg, 35%) as a white, crystalline solid, mp 100–104 °C, $[\alpha]_D$ +82 (c 1.0, $CHCl_3$) (Found: $M^{+\bullet}$, 248.1406; C, 72.67; H, 8.09. $C_{15}H_{20}O_3$ requires $M^{+\bullet}$, 248.1412; C, 72.55; H, 8.12%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.86 (dd, J = 5.7 and 10.2 Hz, 1H), 5.69 (dd, J = 2.2 and 10.2 Hz, 1H), 4.32 (m, 2H), 2.44 (m, 1H), 2.34 (m, 1H), 2.17 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H), 1.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.1 (C), 127.5 (CH), 123.4 (CH), 108.4 (C), 73.4 (CH), 72.4 (CH), 39.6 (C), 36.8 (CH_2), 29.4 (C), 28.0 (CH_3), 26.1 (CH_3), 25.0 (CH_2), 24.3 (CH), 18.5 (CH_2), 9.1 (CH_3). ν_{max} 2959, 2923, 2867, 2838, 1676, 1457, 1377, 1167, 1098, 1046 cm^{-1}. Mass spectrum (EI, 70 eV) 248 ($M^{+\bullet}$, <1%), 233 (5), 191 (18), 161 (100), 147 (23), 134 (21), 121 (44), 105 (48), 91 (55), 84 (50), 77 (25), 55 (30), 49 (48), 43 (72).

Concentration of fraction C (R_f = 0.3 in 3:7 v/v ethyl acetate/hexane) afforded a single diastereoisomeric form of compound **14** (17 mg, 10%) as a clear, colorless oil, $[\alpha]_D$ +374 (c 0.1, $CHCl_3$) (Found: $M^{+\bullet}$, 248.1415. $C_{15}H_{20}O_3$ requires $M^{+\bullet}$, 248.1412). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.86 (dd, J = 5.6 and 9.6 Hz, 1H), 5.69 (dd, J = 4.0 and 9.6 Hz, 1H), 5.75 (d, J = 5.6 Hz, 1H), 4.68 (dd, J = 4.0 and 8.8 Hz, 1H), 4.45 (d, J = 8.8 Hz, 1H), 3.23 (m, 1H), 2.57 (p, J = 7.6 Hz, 1H), 2.42 (m, 1H), 2.29 (m, 1H), 2.02 (m, 2H), 1.40 (s, 3H), 1.39 (s, 3H), 0.86 (d, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.5 (C),

dx.doi.org/10.1021/jo400952u | J. Org. Chem. 2013, 78, 7100–7111

136.9 (C), 124.3 (CH), 123.2 (CH), 119.1 (CH), 105.5 (C), 73.0 (CH), 71.1 (CH), 45.0 (CH), 42.7 (CH_2), 37.2 (CH), 26.8 (CH_3), 24.9 (CH_3), 23.2 (CH_2), 11.0 (CH_3). ν_{max} 2927, 1740, 1455, 1407, 1370, 1211, 1158, 1047 cm^{-1}. Mass spectrum (EI, 70 eV) 248 ($M^{+\bullet}$, 3%), 233 (8), 190 (70), 173 (40), 161 (20), 147 (36), 133 (60), 119 (43), 105 (45), 97 (77), 94 (75), 91 (72), 77 (41), 69 (100), 55 (73), 43 (81).

Method B: A solution of diazoketone **12** (260 mg, 0.94 mmol) and $Cu(acac)_2$ (25 mg, 0.09 mmol, freshly recrystallized from dichloromethane/methanol) in dichloromethane (32 mL) was heated at reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure to give a yellow/blue semisolid that was subjected to flash chromatography (neutral alumina, 1:9 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane) afforded a white solid that, upon recrystallization (hexane/diethyl ether), gave cyclopropane **15** (198 mg, 85%) as a white, crystalline solid. This material was identical, in all respects, with that obtained by Method A as described immediately above.

Compound 18. Method A: A solution of cyclopropane **15** (20 mg, 0.08 mmol) and $Rh(CO)_2(acac)$ (25 mg, 0.08 mmol) in toluene (24 mL) contained in a sealed glass tube was heated at 140 °C for 24 h. The cooled solution was washed with KCN (10 mL of a 20% w/v aqueous solution) and brine (1 × 5 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a clear, colorless oil. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane) afforded compound **18** (11 mg, 55%) as a clear, colorless oil, $[\alpha]_D$ +126 (*c* 0.7, $CHCl_3$) [Found: $(M - CH_3\bullet)^+$, 233.1176. $C_{15}H_{20}O_3$ requires $(M - CH_3\bullet)^+$, 233.1178]. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.90 (dt, *J* = 0.9 and 4.2 Hz, 1H), 5.72 (d, *J* = 1.8 Hz, 1H), 5.47 (dm, *J* = 9.9 Hz, 1H), 5.13 (d, *J* = 1.8 Hz, 1H), 4.33 (m, 1H), 4.15 (dd, *J* = 1.5 and 6.3 Hz, 1H), 2.64 (dm, *J* = 16.8 Hz, 1H), 2.48−2.36 (complex m, 1H), 2.28 (dm, *J* = 12.9 Hz, 1H), 2.20 (m, 2H), 2.16−2.02 (complex m, 1H), 1.97 (m, 1H), 1.72 (m, 1H), 1.41 (s, 3H), 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.9 (C), 148.3 (C), 130.4 (CH), 126.3 (CH), 120.2 (CH_2), 107.8 (C), 76.2 (CH), 71.8 (CH), 45.8 (C), 41.1 (CH_2), 33.6 (CH_2), 29.4 (CH_2), 27.0 (CH_3), 25.0 (CH_3), 19.2 (CH_2). ν_{max} 2918, 2850, 1695, 1609, 1379, 1238, 1213, 1148, 1065, 1044, 1027 cm^{-1}. Mass spectrum (EI, 70 eV) 248 ($M^{+\bullet}$, <1%), 233 (34), 190 (100), 161 (68), 147 (60), 145 (48), 143 (35), 134 (35), 105 (48), 91 (62), 77 (26), 43 (28).

Method B: A solution of cyclopropane **15** (20 mg, 0.08 mmol) in toluene (24 mL) contained in a sealed glass tube was heated at 140 °C for 24 h. The cooled reaction mixture was concentrated under reduced pressure to give a clear, colorless oil that was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) thereby affording, after concentration of the relevant fractions (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane), compound **18** (14 mg, 70%) as a clear, colorless oil. This material was identical, in all respects, with that obtained by Method A as described immediately above.

Method C: Cyclopropane **15** (43 mg, 0.17 mmol) was passed through a horizontally oriented quartz tube (pretreated with a slurry of lead carbonate in water) heated at 600 °C while being maintained at less than 0.1 mmHg.[32] The pyrolyzate, which was trapped with liquid nitrogen, proved to be compound **18** (42 mg, 98%). This clear, colorless oil was identical, in all respects, with that obtained by Method A as described immediately above.

Method D: Cyclopropane **19** (20 mg, 0.08 mmol, prepared as described immediately below) was passed through a horizontally oriented quartz tube (pretreated with a slurry of lead carbonate in water) heated at 600 °C while being maintained at less than 0.1 mmHg. The pyrolyzate, which was trapped with liquid nitrogen, proved to be compound **18** (42 mg, 76%). This clear, colorless oil was identical, in all respects, with that obtained by Method A as described immediately above.

Compound 19. A solution of ketone **15** (58 mg, 0.23 mmol) and $CeCl_3 \cdot 7H_2O$ (174 mg, 0.467 mmol) in MeOH (7 mL) was cooled to 0 °C and then treated, in portions over a 0.5 h period, with $NaBH_4$ (28 mg, 0.75 mmol). The resulting mixture was allowed to warm to 18 °C and stirred at this temperature for 1 h then water (10 mL) was added slowly, and after gas evolution had ceased, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was extracted with dichloromethane (4 × 10 mL), and the combined organic phases were washed with brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford compound **19** (57 mg, 97%) as an approximately 2:1 mixture of diastereoisomers and a clear, colorless oil (R_f = 0.2 in 3:7 v/v ethyl acetate/hexane) (Found: $M^{+\bullet}$, 250.1574. $C_{15}H_{22}O_3$ requires $M^{+\bullet}$, 250.1569). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.88 (m, 1H), 5.48 (d, *J* = 10.5 Hz, 1H), 4.31 (t, *J* = 6.0 Hz, 1H), 4.18 (t, *J* = 6.0 Hz, 1H), 3.97 (m, 0.66H), 3.88 (m, 0.33H), 2.07 (m, 1H), 1.88−1.42 (complex m, 5H), 1.36 (s, 3H), 1.32 (s, 3H), 1.15 (m, 1H), 0.98 (s, 1H), 0.94 (s, 2H), (signal due to alcohol proton not observed). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 125.8 (CH), 125.6 (CH), 124.8 (CH), 124.4 (CH), 107.5 (C), 107.4 (C), 74.9 (CH), 74.8 (CH), 73.2 (CH), 72.4 (CH), 72.3 (CH), 71.4 (CH), 33.5 (C), 31.5 (C), 30.0 (CH_2), 28.1 (CH_2), 28.0 (CH_3), 27.9 (CH_3), 27.0 (CH_2), 26.3 (C), 26.2 (CH_3), 26.0 (CH_3), 25.2 (CH_2), 24.8 (CH), 23.7 (C), 22.2 (CH), 19.9 (CH_2), 14.9 (CH_2), 14.3 (CH_3), 12.8 (CH_3). ν_{max} 3400, 2982, 2931, 2872, 1455, 1369, 1236, 1180, 1163, 1142, 1129, 1047 cm^{-1}. Mass spectrum (EI, 70 eV) 250 ($M^{+\bullet}$, <1%), 235 (1), 192 (18), 175 (19), 159 (23), 145 (70), 131 (25), 121 (89), 120 (100), 108 (55), 107 (50), 91 (47), 85 (47), 77 (31), 55 (30), 43 (69).

Compound 20. A magnetically stirred solution of alcohol **19** (20 mg, 0.08 mmol) in THF (0.5 mL) maintained at 18 °C was treated with NaH (5.4 mg of a 60% dispersion in mineral oil, 0.14 mmol). After 0.5 h, the reaction mixture was treated with carbon disulfide (5 μL, 0.088 mmol), and after a further 0.5 h, the reaction mixture was cooled to 0 °C and then treated with iodomethane (6 μL, 0.088 mmol). The ensuing mixture was then warmed to 18 °C and stirred at this temperature for 2 h before being quenched with NH_4Cl (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic phases were washed with brine (1 × 15 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.6 in 3:7 v/v ethyl acetate/hexane) afforded compound **20** (20 mg, 74%) as a 2:1 mixture of diastereoisomers and as a clear, colorless oil (Found: $M^{+\bullet}$, 340.1169. $C_{17}H_{24}O_3S_2$ requires $M^{+\bullet}$, 340.1167). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.87 (m, 1H), 5.50 (m, 1H), 4.37−3.95 (complex m, 3H), 2.42 (s, 2H), 2.41 (s, 1H), 2.10−1.40 (complex m, 7H), 1.35 (s, 3H), 1.32 (s, 3H), 0.94 (s, 1H), 0.93 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.1 (C), 189.7 (C), 125.5 (CH), 125.4 (CH), 125.2 (CH), 124.6 (CH), 107.7 (C), 107.6 (C), 74.5 (CH), 73.7 (CH), 72.3 (CH), 72.2 (CH), 50.9 (CH), 50.7 (CH), 30.3 (CH_2), 29.5 (C), 29.3 (C), 27.9 (CH_3), 27.8 (CH_3), 26.9 (CH_2), 26.2 (CH_2), 26.1(3) (CH_3), 26.0(9) (CH_3), 26.0 (C), 24.4 (C), 24.3 (CH_2), 24.2 (CH), 23.6 (CH), 20.5 (CH_2), 16.2 (CH_2), 15.4 (CH_3), 14.7 (CH_3), 13.1 (CH_3), 13.0 (CH_3). ν_{max} 2982, 2930, 2855, 1738, 1710, 1643, 1457, 1377, 1368, 1236, 1218, 1165, 1145, 1051, 865 cm^{-1}. Mass spectrum (EI, 70 eV) 340 ($M^{+\bullet}$, 12%), 282 (91), 207 (81), 175 (100), 165 (39), 147 (66), 145 (63), 133 (40), 107 (63), 105 (61), 91 (71), 81 (60), 75 (52), 55 (43), 43 (51).

Compounds 21 and 22. Method A: 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine[9] (229 μL, 1.73 mmol) was added to a magnetically stirred solution of acid **11** (414 mg, 1.73 mmol) in dichloromethane (21 mL), and the resulting solution cooled to 0 °C. An excess of ethereal diazomethane[8] was added to the reaction mixture that was then allowed to warm to 18 °C and stirred at this temperature for 0.25 h before being concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) gave two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 3:7 v/v ethyl acetate/hexane) afforded compound **22** (83 mg, 18%) as a clear, colorless oil, $[\alpha]_D$ +107 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.95 (dd, *J* = 5.7 and 9.6 Hz, 1H), 5.78 (dd, *J* = 3.9 and 9.6 Hz, 1H), 5.71 (d, *J* = 5.7 Hz, 1H), 4.64 (dd, *J* = 3.9 and 8.7 Hz, 1H), 4.49 (d, *J* = 8.7 Hz, 1H), 4.07 (s, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.22 (m, 2H), 1.84 (m,

dx.doi.org/10.1021/jo400952u | J. Org. Chem. 2013, 78, 7100−7111

2H), 1.38 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.3 (C), 137.0 (C), 124.3 (CH), 123.0 (CH), 119.0 (CH), 105.1 (C), 73.0 (CH), 71.2 (CH), 48.2 (CH_2), 39.0 (CH_2), 32.8 (CH_2), 26.8 (CH_3), 24.9 (CH_3), 20.9 (CH_2). ν_{max} 2984, 2919, 1734, 1402, 1370, 1209, 1158, 1026, 868 cm^{-1}. Mass spectrum (EI, 70 eV) 257 and 255 (each <1%), 212 (8) 195 (28), 120 (100), 107 (59), 91 (36), 77 (43), 43 (48). The unstable nature of this compound prevented the acquisition of HRMS or microanalytical data.

Concentration of fraction B (R_f = 0.2 in 3:7 v/v ethyl acetate/hexane) afforded compound **21** (320 mg, 71%) as a clear, yellow oil, $[\alpha]_D$ +127 (*c* 1.2, $CHCl_3$) [Found: $(M + Na)^+$, 285.1215. $C_{14}H_{18}N_2O_3$ requires $(M + Na)^+$, 285.1215]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92 (dd, *J* = 5.4 and 9.9 Hz, 1H), 5.74 (dd, *J* = 3.6 and 9.9 Hz, 1H), 5.78 (d, *J* = 5.4 Hz, 1H), 5.25 (s, 1H), 4.61 (dd, *J* = 3.6 and 9.0 Hz, 1H), 4.47 (d, *J* = 9.0 Hz, 1H), 2.33 (m, 4H), 1.81 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.8 (C), 137.2 (C), 124.4 (CH), 122.9 (CH), 119.0 (CH), 105.1 (C), 73.1 (CH), 71.2 (CH), 54.4 (CH), 40.3 (CH_2), 33.0 (CH_2), 26.8 (CH_3), 25.0 (CH_3), 22.6 (CH_2). ν_{max} 2986, 2929, 2101, 1639, 1371, 1322, 1207, 1157, 1142, 1025, 891, 867 cm^{-1}. Mass spectrum (EI, 70 eV) 262 ($M^{+\bullet}$, <1%), 256 (9), 187 (81), 175 (12), 159 (17), 147 (23), 133 (33), 121 (60), 120 (53), 107 (89), 91 (72), 77 (50), 55 (100), 43 (85).

Method B: 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine[9] (162 μL, 1.22 mmol) was added to a magnetically stirred solution of acid **11** (292 mg, 1.22 mmol) in dichloromethane (14 mL) maintained at 18 °C. After 0.08 h the reaction mixture was treated with 4-(*N*,*N*-dimethylamino)pyridine (298 mg, 2.44 mmol), and the resulting solution was cooled to 0 °C and treated with an excess of ethereal diazomethane[8] before being warmed to 18 °C and then stirred at this temperature for 0.25 h. The ensuing mixture was concentrated under reduced pressure to give a yellow semisolid that was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane) affording, after concentration of the relevant fractions (R_f = 0.2 in 3:7 v/v ethyl acetate/hexane), compound **21** (292 mg, 91%) as clear, yellow oil. This material was identical, in all respects, with that obtained via Method A as described immediately above.

Compounds 23−25. Method A: A solution of diazoketone **21** (139 mg, 0.53 mmol) and $Cu(acac)_2$ (14 mg, 0.05 mmol, freshly recrystallized from dichloromethane/methanol) in dichloromethane (53 mL) was heated at reflux for 18 h, cooled, and concentrated under reduced pressure to give a yellow/blue semisolid. Subjection of this material to flash chromatography (neutral alumina, 1:9 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A [R_f = 0.1(8) in 3:7 v/v ethyl acetate/hexane] afforded a white solid that was recrystallized (hexane−diethyl ether) to give cyclopropane **23** (98 mg, 79%) as a white, crystalline solid, mp 88−90 °C, $[\alpha]_D$ +293 (*c* 1.2 in $CHCl_3$) (Found: $M^{+\bullet}$, 234.1259; C, 71.75; H 7.77. $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256; C, 71.77; H, 7.74%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.99 (m, 1H), 5.37 (d, *J* = 9.9 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 1H), 4.34 (dt, *J* = 1.8 and 6.0 Hz, 1H), 2.30 (m, 3H), 2.12−1.74 (complex m, 3H), 1.65 (m, 1H), 1.51 (d, *J* = 3.3 Hz, 1H), 1.35 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.0 (C), 126.0 (CH), 125.8 (CH), 109.7 (C), 74.7 (CH), 71.6 (CH), 42.0 (CH), 36.3 (CH_2), 28.3 (CH_3), 27.0 (C), 26.6 (CH_3), 24.5 (CH_2), 22.0 (CH), 17.4 (CH_2). ν_{max} 2918, 2850, 1687, 1455, 1368, 1235, 1181, 1142, 1129, 1093, 1075, 1057, 933, 867 cm^{-1}. Mass spectrum (EI, 70 eV) 234 ($M^{+\bullet}$, 1%), 219 (5), 177 (20), 147 (100), 131 (20), 120 (30), 107 (42), 91 (55), 43 (34).

Concentration of fraction B [R_f = 0.1(5) in 3:7 v/v ethyl acetate/hexane] afforded compound **24** (12 mg, 10%) as a clear, colorless oil, $[\alpha]_D$ −59 (*c* 1.2, $CHCl_3$) (Found: $M^{+\bullet}$, 234.1257. $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.35 (dd, *J* = 4.8 and 9.9 Hz, 1H), 5.74 (dd, *J* = 5.4 and 9.9 Hz, 1H), 4.56 (m, 1H), 4.26 (d, *J* = 7.2 Hz, 1H), 2.38−1.98 (complex m, 5H), 1.98 (d, *J* = 3.6 Hz, 1H), 1.80 (m, 1H), 1.64 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.5 (C), 132.3 (CH), 121.7 (CH), 107.5 (C), 75.3 (CH), 70.1 (CH), 45.9 (CH), 36.0 (CH_2), 27.7 (CH_3), 26.3 (CH_2), 25.5 (CH), 25.0 (CH_3), 22.3 (C), 17.3 (CH_2). ν_{max} 2984, 2922, 2853, 1682, 1455, 1379, 1246, 1212, 1156, 1107, 1045, 1027, 910, 872 cm^{-1}. Mass spectrum (EI, 70 eV) 234 ($M^{+\bullet}$, 12%), 219 (6), 177 (40), 176 (42), 159 (43), 147 (100), 131 (25), 120 (28), 91 (72), 55 (42), 43 (78). This material was contaminated with small amounts of isomer **23**.

Method B: A deoxygenated solution of compound **21** (299 mg, 1.14 mmol) and acetophenone (666 μL, 5.70 mmol) in acetone (350 mL) was placed in a quartz immersion-well photoreactor (500 mL) equipped with a borosilicate glass filter. This was subjected to irradiation with a 450 W medium pressure quartz mercury-vapor lamp for 1 h before being cooled and concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash chromatography (silica, 5:95 → 3:7 v/v ethyl acetate/hexane gradient elution) affording two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane) afforded compound **25** (29 mg, 11%) as a low-melting solid, $[\alpha]_D$ +19 (*c* 0.8, $CHCl_3$) (Found: $M^{+\bullet}$, 234.1257. $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76 (dd, *J* = 2.4 and 9.9 Hz, 1H), 5.65 (dd, *J* = 3.0 and 9.9 Hz, 1H), 4.60 (m, 1H), 4.26 (d, *J* = 6.6 Hz, 1H), 2.80 (t, *J* = 3.6 Hz, 1H), 2.56 (m, 2H), 2.29 (m, 3H), 1.88 (m, 1H), 1.70 (m, 1H), 1.37 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.7 (C), 128.4 (CH), 126.9 (CH), 109.3 (C), 71.7 (CH), 70.9 (CH), 63.9 (C), 61.4 (CH), 35.9 (CH_2), 34.6 (CH), 33.1 (CH_2), 28.0 (CH_3), 26.4 (CH_3), 17.9 (CH_2). ν_{max} 2983, 2932, 2867, 1775, 1452, 1377, 1224, 1032 cm^{-1}. Mass spectrum (EI, 70 eV) 234 ($M^{+\bullet}$, <1%), 219 (10), 176 (38), 147 (26), 120 (22), 91 (30), 87 (72), 71 (100).

Concentration of fraction B (R_f = 0.3 in 3:7 v/v ethyl acetate/hexane) afforded compound **23** (162 mg, 61%) as a white, crystalline solid. This material was identical, in all respects, with that obtained via Method A described immediately above.

Compounds 25 and 26. A deoxygenated solution of compound **21** (40 mg, 0.15 mmol) in 1,4-dioxane (4 mL) and hexane (350 mL) was placed in a quartz immersion-well photoreactor (500 mL) equipped with a borosilicate glass filter. This was subjected to irradiation with a 450 W medium-pressure quartz mercury-vapor lamp for 0.33 h and then transferred to a round-bottom flask and heated at 100 °C for 2.5 h. Methanol (5 mL) was then added to the partially cooled reaction mixture that was then cooled to 18 °C and concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash chromatography (silica, 5:95 → 3:7 v/v ethyl acetate/hexane gradient elution) affording two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 3:7 v/v ethyl acetate/hexane) afforded compound **26** (11 mg, 31%) as a clear, colorless oil, $[\alpha]_D$ +89 (*c* 0.9, $CHCl_3$) (Found: $M^{+\bullet}$, 234.1261. $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.27 (dd, *J* = 5.1 and 8.1 Hz, 1H), 6.08 (d, *J* = 8.1 Hz, 1H), 4.95 (t, *J* = 4.2 Hz, 1H), 4.79 (m, 1H), 4.47 (m, 1H), 4.18 (dd, *J* = 1.2 and 7.2 Hz, 1H), 2.16−1.92 (complex m, 4H), 1.62 (m, 2H), 1.32 (s, 3H), 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.9 (C), 137.1 (CH), 127.9 (CH), 110.4 (C), 97.4 (CH), 77.2 (CH), 76.5 (CH), 70.2 (CH), 42.8 (C), 30.2 (CH_2), 25.6 (CH_3), 25.5 (CH_3), 23.6 (CH_2), 19.7 (CH_2). ν_{max} 2926, 2855, 1681, 1456, 1379, 1264, 1234, 1208, 1162, 1123, 1084, 1050, 981, 900, 862 cm^{-1}. Mass spectrum (EI, 70 eV) 234 ($M^{+\bullet}$, <1%), 219 (10), 176 (38), 165 (29), 149 (40), 135 (65), 134 (100), 120 (20), 107 (35), 91 (33), 81 (27), 69 (38), 55 (50), 43 (73).

Concentration of fraction B (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane) afforded compound **25** (7 mg, 20%) as a low-melting solid. This material was identical, in all respects, with that obtained via the method described earlier.

Compounds 15 and 27. A deoxygenated solution of compound **12** (84 mg, 0.30 mmol) and acetophenone (178 μL, 1.52 mmol) in acetone (350 mL) was placed in a quartz immersion-well photoreactor (500 mL) equipped with a borosilicate glass filter. This was subjected to irradiation with a 450 W medium-pressure quartz mercury-vapor lamp for 1 h and then cooled and concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash chromatography (silica, 5:95 → 3:7 v/v ethyl acetate/hexane gradient elution) affording two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 3:7 v/v ethyl acetate/hexane) afforded compound **27** (5 mg, 6%) as a white, crystalline solid, mp 51−53 °C, $[\alpha]_D$ +8 (*c* 0.5, $CHCl_3$) (Found: $M^{+\bullet}$, 248.1403.

dx.doi.org/10.1021/jo400952u | J. Org. Chem. 2013, 78, 7100−7111

$C_{15}H_{20}O_3$ requires $M^{+\bullet}$, 248.1412). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.69 (m, 2H), 4.56 (dd, J = 2.4 and 5.7 Hz, 1H), 4.29 (d, J = 5.7 Hz, 1H), 2.57 (m, 1H), 2.50 (m, 1H), 2.32−2.06 (complex m, 3H), 1.88 (m, 1H), 1.68 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 0.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.8 (C), 129.1 (CH), 124.8 (CH), 109.2 (C), 71.7 (CH), 70.8 (CH), 65.3 (C), 62.5 (C), 40.8 (CH_2), 37.5 (CH), 35.4 (CH_2), 28.1 (CH_3), 26.5 (CH_3), 18.1 (CH_2), 14.1 (CH_3). ν_{max} 2925, 2856, 1771, 1446, 1377, 1236, 1180, 1163, 1142, 1091, 1050, 864 cm^{-1}. Mass spectrum (EI, 70 eV) 248 ($M^{+\bullet}$, 6%), 205 (10), 161 (23), 149 (50), 148 (100), 133 (24), 105 (46), 91 (26), 77 (28), 69 (43), 57 (47), 43 (73).

Concentration of fraction B (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane) afforded compound **15** (49 mg, 63%) as a white, crystalline solid. This material was identical, in all respects, with that obtained via the methods described earlier.

Compounds 27 and 28. A deoxygenated solution of compound **12** (64 mg, 0.26 mmol) in 1,4-dioxane (5 mL) and hexane (350 mL) was placed in a quartz immersion-well photoreactor (500 mL) equipped with a borosilicate glass filter. This was subjected to irradiation with a 450 W medium-pressure quartz mercury-vapor lamp for 1 h. Methanol (5 mL) was then added to the solution that was concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash chromatography (silica, 5:95 → 3:7 v/v ethyl acetate/hexane gradient elution) affording two fractions, A and B.

Concentration of fraction A [R_f = 0.5(4) in 3:7 ethyl acetate/hexane] afforded compound **28** (20 mg, 35%) as a clear, colorless oil, $[\alpha]_D$ +70 (c 0.6, $CHCl_3$) (Found: $M^{+\bullet}$, 248.1428. $C_{15}H_{20}O_3$ requires $M^{+\bullet}$, 248.1412). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.26 (dd, J = 5.1 and 8.1 Hz, 1H), 6.06 (d, J = 8.1 Hz, 1H), 4.82 (m, 1H), 4.45 (dd, J = 4.2 and 6.9 Hz, 1H), 4.14 (d, J = 6.9 Hz, 1H), 2.07 (m, 1H), 1.94 (m, 3H), 1.62 (m, 2H), 1.56 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.8 (C), 137.2 (CH), 127.8 (CH), 110.2 (C), 105.4 (C), 77.5 (CH), 76.6 (CH), 70.0 (CH), 42.6 (C), 30.6 (CH_2), 30.1 (CH_3), 25.6 (CH_2), 25.5 (CH_3), 19.7 (CH_2), 16.0 (CH_3). ν_{max} 2926, 1697, 1453, 1378, 1207, 1117, 1079, 1058, 985, 919 cm^{-1}. Mass spectrum (EI, 70 eV) 248 ($M^{+\bullet}$, 41%), 233 (21), 190 (10), 175 (12), 163 (37), 161 (54), 149 (47), 148 (100), 133 (66), 119 (18), 107 (49).

Concentration of fraction B [R_f = 0.5(0) in 3:7 v/v ethyl acetate/hexane] afforded compound **27** (20 mg, 35%) as a white, crystalline solid. This material was identical, in all respects, with that obtained via the method described immediately above.

Compound 31. Zinc dust (870 mg, 13.3 mmol) maintained under nitrogen was treated with iodine chips (113 mg, 0.44 mmol), and the ensuing mixture was stirred for 0.03 h and then diluted with *N,N*-dimethylacetamide (5 mL). A solution of iodide **29** (2.15 g, 8.88 mmol) in *N,N*-dimethylacetamide (5 mL) was added to the reaction mixture that was then stirred at 80 °C for 3 h before being allowed to cool to 50 °C. A solution of $Pd(PPh_3)_4$ (614 mg, 0.53 mmol) in *N,N*-dimethylacetamide (5 mL) was added to the ensuing mixture, and after stirring this for 0.08 h, a solution of acetonide **7** (1.48 g, 5.32 mmol) in *N,N*-dimethylacetamide (3 mL) was introduced. The resulting mixture was stirred at 50 °C for 2 h before being cooled and then quenched with $NaHCO_3$ (25 mL of a saturated aqueous solution). The resulting mixture was filtered through diatomaceous earth, and the separated aqueous phase associated with the filtrate was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were then washed with brine (1 × 25 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:99 → 1:9 v/v ethyl acetate/hexane gradient elution), and concentration of the relevant fractions (R_f = 0.5 in 3:7 v/v ethyl acetate/hexane) afforded compound **31** (1.05 g, 74%) as a clear, colorless oil, $[\alpha]_D$ +62 (c 0.6, $CHCl_3$) [Found: $(M - CH_3\bullet)^+$, 251.1280. $C_{15}H_{22}O_4$ requires $(M - CH_3\bullet)^+$, 251.1283]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.97 (dd, J = 5.7 and 9.6 Hz, 1H), 5.78 (dd, J = 3.9 and 9.6 Hz, 1H), 5.71 (d, J = 5.7 Hz, 1H), 4.64 (dd, J = 3.9 and 8.7 Hz, 1H), 4.52 (d, J = 8.7 Hz, 1H), 3.66 (s, 3H), 2.33 (t, J = 6.9 Hz, 2H), 2.23 (m, 2H), 1.72−1.48 (complex m, 4H), 1.40 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0 (C), 138.0 (C), 124.7 (CH), 122.6 (CH), 118.4 (CH), 105.2 (C), 73.3 (CH), 71.2 (CH), 51.5 (CH_3), 33.9 (CH_2), 33.1 (CH_2), 26.9 (CH_3), 26.6 (CH_2), 25.1 (CH_3), 24.6 (CH_2). ν_{max} 2933, 1739, 1434, 1370, 1209, 1160, 1046 cm^{-1}. Mass spectrum (EI, 70 eV) 251 [$(M - CH_3\bullet)^+$, 2%), 208 (26), 177 (96), 176 (100), 158 (26), 133 (40), 120 (72), 107 (88), 91 (57), 77 (40), 59 (31), 43 (55).

Compound 32. DIBAL-H (1.22 mL of a 1.0 M solution in hexanes, 1.22 mmol) was added dropwise to a solution of ester **31** (326 mg, 1.22 mmol) in dichloromethane (10 mL) maintained at −78 °C. The ensuing mixture was stirred at −78 °C for 0.75 h, a few drops of methanol were added, and the solution was allowed to warm to 18 °C. Water (15 mL) was then added, and the resulting solution was filtered through diatomaceous earth and extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with brine (1 × 15 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford aldehyde **32** (288 mg, 100%) as a clear, yellow oil, $[\alpha]_D$ +95 (c 0.9, $CHCl_3$) (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane) [Found: $(M - CH_3\bullet)^+$, 221.1175. $C_{14}H_{20}O_3$ requires $(M - CH_3\bullet)^+$, 221.1178]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.77 (t, J = 1.5 Hz, 1H), 5.98 (dd, J = 5.4 and 9.6 Hz, 1H), 5.80 (dd, J = 3.6 and 9.6 Hz, 1H), 5.71 (d, J = 5.4 Hz, 1H), 4.65 (dd, J = 3.6 and 8.4 Hz, 1H), 4.52 (d, J = 8.4 Hz, 1H), 2.47 (dt, J = 1.5 and 6.9 Hz, 2H), 2.25 (m, 2H), 1.72−1.42 (complex m, 4H), 1.40 (s, 3H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.8 (CH), 137.1 (C), 125.1 (CH), 122.9 (CH), 118.8 (CH), 105.5 (C), 73.6 (CH), 71.5 (CH), 44.0 (CH_2), 33.6 (CH_2), 27.1 (CH_3), 26.9 (CH_2), 25.3 (CH_3), 22.0 (CH_2). ν_{max} 2984, 2932, 1725, 1459, 1370, 1235, 1209, 1159, 1047 cm^{-1}. Mass spectrum (ESI) 221 [$(M - CH_3\bullet)^+$, 2%], 178 (14), 161 (71), 160 (73), 145 (20), 133 (20), 121 (28), 107 (100), 91 (53), 79 (46), 77 (47), 43 (80).

Compounds 33 and 34. *Step (i).* A magnetically stirred solution of aldehyde **32** (293 mg, 1.24 mmol) in water (3 mL) was cooled to 0 °C and then treated with sodium carbonate (263 mg, 2.48 mmol) and hydroxylamine hydrochloride (164 mg, 2.36 mmol). The resulting solution was stirred at 0 °C for 3 h and then diluted with ethyl acetate (5 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the rather unstable oxime **33** (270 mg, 87%) as a clear, colorless oil and an approximately 1:1 mixture of *E* and *Z* isomers (R_f = 0.2 in 3:7 v/v ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (br s, 1H), 7.42 (t, J = 6.3 Hz, 0.5H), 6.72 (t, J = 5.1 Hz, 0.5H), 5.97 (dd, J = 5.4 and 9.6 Hz, 1H), 5.89 (dd, J = 3.9 and 9.6 Hz, 1H), 5.71 (d, J = 5.4 Hz, 1H), 4.65 (dd, J = 3.9 and 8.7 Hz, 1H), 4.52 (d, J = 8.7 Hz, 1H), 2.40 (m, 1H), 2.22 (m, 3H), 1.54 (m, 4H), 1.41 (s, 3H), 1.38 (s, 3H). ν_{max} 3385, 2989, 2932, 2861, 1601, 1370, 1210, 1158, 1048 cm^{-1}. Mass spectrum (EI, 70 ev) 236 [$(M - CH_3\bullet)^+$, 6%), 176 (83), 160 (17), 145 (20) 133 (73), 117 (29), 107 (100), 91 (61), 77 (50), 56 (37), 43 (78). This unstable material was subjected, without further characterization, to step (ii) of the reaction sequence as described immediately below.

Step (ii). Method A: *N*-Chlorosuccinimide (143 mg, 1.07 mmol) was added to a magnetically stirred solution of oxime **33** (270 mg, 1.07 mmol) in chloroform (27 mL). A solution of triethylamine (1.04 mL, 7.49 mmol) in chloroform (5 mL) was then added, and the resulting mixture allowed to stir at 18 °C for 6 h and then quenched with NH_4Cl (30 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were washed with brine (1 × 25 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f = 0.3 in 3:7 v/v ethyl acetate/hexane) afforded isoxazoline **34** (218 mg, 82%) as a white, crystalline solid, mp 122−125 °C, $[\alpha]_D$ −313 (c 0.5, $CHCl_3$) (Found: $M^{+\bullet}$, 249.1365; C, 67.39; H, 7.47; N, 5.55. $C_{14}H_{19}NO_3$ requires $M^{+\bullet}$, 249.1365; C, 67.45; H, 7.68, N, 5.62%]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74 (m, 2H), 4.61 (m, 2H), 4.44 (m, 1H), 2.72 (dd, J = 4.2 and 13.2 Hz, 1H), 2.37 (m, 1H), 2.23 (m, 1H), 2.12 (m, 1H), 1.83−1.52 (complex m, 4H), 1.39 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1 (C), 129.7

dx.doi.org/10.1021/jo400952u | J. Org. Chem. 2013, 78, 7100−7111

(CH), 124.1 (CH), 109.2 (C), 79.3 (CH), 71.5 (CH), 71.4 (CH), 54.0 (C), 35.9 (CH_2), 29.7 (CH_2), 28.2 (CH_3), 27.0 (CH_3), 24.6 (CH_2), 20.8 (CH_2). ν_{max} 2931, 2858, 1624, 1448, 1379, 1369, 1237, 1163, 1078, 1055, 1033 cm^{-1}. Mass spectrum (EI, 70 eV) 249 ($M^{+\bullet}$, 24%), 234 (13), 219 (20), 192 (30), 191 (39), 162 (100), 134 (44), 107 (30), 95 (30), 91 (46), 77 (27), 55 (44), 43 (72).

Method B: A solution of (diacetoxyiodo)benzene (58 mg, 0.18 mmol) and trifluoroacetic acid (5 μL, 0.07 mmol) in methanol (0.4 mL) was added to a magnetically stirred solution of oxime **33** (35 mg, 0.14 mmol) in methanol (0.8 mL). The ensuing mixture was stirred for 0.75 h at 18 °C and then treated with $NaHCO_3$ (2 mL of a saturated aqueous solution) and $NaHSO_3$ (2 mL of a 5% w/v aqueous solution). The resulting mixture was extracted with diethyl ether (3 × 3 mL) and the combined organic phases were washed with brine (1 × 5 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) to afford isoxazoline **34** (24 mg, 70%) as a white, crystalline solid. This material was identical, in all respects, with that obtained via Method A described immediately above.

Compound 35. Method A: A magnetically stirred solution of isoxazoline **34** (40 mg, 0.16 mmol) in ethanol/water (2.6 mL of a 1:1 v/v mixture) was treated with ammonium chloride (84 mg, 1.6 mmol) and then iron powder (89 mg, 1.6 mmol). The ensuing mixture was stirred at 80 °C for 6 h before being allowed to cool and then diluted with ethyl acetate (10 mL). The resulting mixture was filtered through a pad of TLC-grade silica gel, and the filtrate was washed with brine (1 × 5 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.2 in 3:7 v/v ethyl acetate/hexane) afforded compound **35** (28 mg, 70%) as a clear, colorless oil, $[\alpha]_D$ +56 (*c* 0.5, $CHCl_3$) (Found: $M^{+\bullet}$, 252.1367. $C_{14}H_{20}O_4$ requires $M^{+\bullet}$, 252.1362). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.91 (m, 1H), 5.57 (dm, *J* = 10.2 Hz, 1H), 4.73 (d, *J* = 5.1 Hz, 1H), 4.40 (m, 1H), 4.05 (dd, *J* = 2.1 and 11.1 Hz, 1H), 2.93 (d, *J* = 11.1 Hz, 1H), 2.52 (m, 1H), 2.38 (m, 1H), 2.23 (m, 2H), 2.08 (m, 1H), 2.01−1.71 (complex m, 3H), 1.38 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.7 (C), 132.8 (CH), 125.2 (CH), 108.9 (C), 74.7 (CH), 71.4 (CH), 69.7 (CH), 58.2 (C), 40.8 (CH_2), 33.2 (CH_2), 28.0 (CH_2), 27.5 (CH_3), 26.5 (CH_3), 20.3 (CH_2). ν_{max} 3441, 2935, 2867, 1697, 1451, 1379, 1229, 1163, 1096, 1056, 1027 cm^{-1}. Mass spectrum (EI, 70 eV) 252 ($M^{+\bullet}$, 1%), 237 (30), 194 (10), 177 (80), 176 (85), 167 (100), 149 (31), 133 (60), 125 (72), 120 (65), 107 (86), 81 (53), 55 (52), 43 (77).

Method B: A mixture of isoxazoline **34** (123 mg, 0.49 mmol) and $Mo(CO)_6$ (130 mg, 0.49 mmol) was treated with water (355 μL, 19.6 mmol) and acetonitrile (10 mL). The resulting solution was heated at 80 °C with magnetic stirring for 18 h and then cooled and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.2 in 3:7 v/v ethyl acetate/hexane), compound **35** (101 mg, 82%) as a clear, colorless oil. This material was identical, in all respects, with that obtained via Method A described immediately above.

Compound 36. A magnetically stirred solution of hydroxyketone **35** (91 mg, 0.36 mmol) in THF (5 mL) was cooled to 0 °C and then treated with NaH (10 mg, 0.43 mmol). The ensuing mixture was stirred at 0 °C for 3 h and then treated with NH_4Cl (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (3 × 5 mL), and the combined organic phases were washed with brine (1 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. This material was subjected to flash chromatography (silica, 1:99 → 1:9 v/v ethyl acetate/hexane gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.2 in 3:7 v/v ethyl acetate/hexane) afforded the starting hydroxy ketone **35** (43 mg, 23% recovery) as a clear, colorless oil. This material was identical, in all resects, with an authentic sample.

Concentration of fraction B (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane) afforded compound **36** (61 mg, 35%) as a clear colorless oil, $[\alpha]_D$ −49 (*c* 0.3, $CHCl_3$) [Found: $(M - CH_3\bullet)^+$, 237.1129. $C_{14}H_{20}O_4$ requires $(M - CH_3\bullet)^+$, 237.1127]. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.93 (dd, *J* = 5.4 and 10.2 Hz, 1H), 5.69 (ddd, *J* = 1.2, 3.0, and 10.2 Hz, 1H), 4.93 (m, 1H), 4.41 (m, 1H), 4.30 (m, 1H), 3.18 (dd, *J* = 11.4 Hz, 1H), 2.76 (dm, *J* = 13.2 Hz, 1H), 2.51 (m, 1H), 2.30 (m, 1H), 2.12 (m, 1H), 1.96 (m, 1H), 1.72 (m, 2H), 1.60 (m, 1H), 1.43 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.1 (C), 128.9 (CH), 127.7 (CH), 109.0 (C), 78.9 (CH), 72.5 (CH), 65.7 (CH), 56.4 (C), 39.5 (CH_2), 34.9 (CH_2), 28.5 (CH_2), 28.4 (CH_3), 26.6 (CH_3), 20.2 (CH_2). ν_{max} 3527, 2928, 2855, 1706, 1453, 1380, 1234, 1163, 1126, 1088, 1039 cm^{-1}. Mass spectrum (EI, 70 eV) 252 ($M^{+\bullet}$, <1%), 237 (90), 195 (24), 177 (92), 176 (80), 167 (100), 149 (36), 133 (68), 125 (66), 107 (98), 81 (46), 55 (57), 43 (87).

Compound 37. Lithium aluminum hydride (1.81 mL of a 1.0 M solution in THF, 1.81 mmol) was added dropwise to a magnetically stirred solution of ester **10** (208 mg, 0.824 mmol) in THF (17 mL) maintained at −78 °C. The ensuing mixture was warmed to 18 °C, stirred at this temperature for 0.5 h and then treated sequentially with methanol (three drops) and water (15 mL). The resulting mixture was filtered through diatomaceous earth and the filtrate was extracted with diethyl ether (2 × 10 mL). The combined organic phases were washed with brine (1 × 15 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford alcohol **37** (157 mg, 85%) as a clear, colorless oil, $[\alpha]_D$ +136 (*c* 1.4, $CHCl_3$) (R_f = 0.1 in 3:7 v/v ethyl acetate/hexane) [Found: $(M - CH_3\bullet)^+$, 209.1178. $C_{13}H_{20}O_3$ requires $(M - CH_3\bullet)^+$, 209.1178]. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.95 (dd, *J* = 5.4 and 9.6 Hz, 1H), 5.76 (dd, *J* = 3.9 and 9.6 Hz, 1H), 5.70 (d, *J* = 5.4 Hz, 1H), 4.64 (dd, *J* = 3.9 and 8.7 Hz, 1H), 4.51 (d, *J* = 8.7 Hz, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 2.23 (m, 2H), 1.88 (m, 1H), 1.58 (m, 4H), 1.39 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.1 (C), 124.7 (CH), 122.6 (CH), 118.5 (CH), 105.3 (C), 73.4 (CH), 71.3 (CH), 62.5 (CH_2), 33.3 (CH_2), 32.3 (CH_2), 26.9 (CH_3), 25.1 (CH_3), 23.3 (CH_2). ν_{max} 3422, 2985, 2934, 2871, 1660, 1602, 1456, 1432, 1402, 1378, 1370, 1235, 1209, 1158, 1048, 958, 884 cm^{-1}. Mass spectrum (EI, 70 eV) 209 [$(M - CH_3\bullet)^+$, 2%], 166 (72), 149 (78), 133 (60), 120 (69), 107 (100), 91 (66), 77 (62), 55 (54), 43 (90).

Compound 38. A magnetically stirred solution of alcohol **37** (110 mg, 0.49 mmol) and triethylamine (82 μL, 0.59 mmol) in diethyl ether (7 mL) was cooled to 0 °C then treated, dropwise, with methanesulfonyl chloride (45 μL, 0.59 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 2 h before being diluted with diethyl ether (20 mL) and washed with water (2 × 25 mL). The combined aqueous phases were extracted with diethyl ether (1 × 50 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the mesylate **38** (148 mg, 100%) as a clear, colorless oil, $[\alpha]_D$ +86 (*c* 1.0, $CHCl_3$) (R_f = 0.2 in 3:7 v/v ethyl acetate/hexane) [Found: $(M - CH_3\bullet)^+$, 287.0953. $C_{14}H_{22}O_5S$ requires $(M - CH_3\bullet)^+$, 287.0953]. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.95 (dd, *J* = 6.0 and 9.3 Hz, 1H), 5.77 (dd, *J* = 3.9 and 9.3 Hz, 1H), 5.69 (d, *J* = 6.0 Hz, 1H), 4.63 (dd, *J* = 3.9 and 8.7 Hz, 1H), 4.49 (d, *J* = 8.7 Hz, 1H), 4.22 (t, *J* = 6.3 Hz, 2H), 2.98 (s, 3H), 2.24 (m, 2H), 1.76 (m, 2H), 1.62 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3 (C), 124.4 (CH), 122.7 (CH), 118.6 (CH), 105.1 (C), 73.1 (CH), 71.1 (CH), 69.7 (CH_2), 37.2 (CH_3), 32.8 (CH_2), 28.7 (CH_2), 26.8 (CH_3), 24.9 (CH_3), 23.0 (CH_2). ν_{max} 2984, 2934, 1660, 1602, 1457, 1353, 1258, 1235, 1208, 1173, 1044, 1024, 974, 935 cm^{-1}. Mass spectrum (EI, 70 eV) 302 ($M^{+\bullet}$, <1%), 287 [$(M-CH_3\bullet)^+$, 3], 244 (47), 191 (10), 149 (69), 148 (63), 133 (60), 120 (69), 107 (67), 91 (60), 79 (100), 65 (30), 55 (54), 43 (65).

Compound 39. A magnetically stirred solution of mesylate **38** (90 mg, 0.30 mmol) in DMF (2.5 mL) maintained at 18 °C was treated with sodium azide (58 mg, 0.89 mmol) and the resulting solution was heated at 50 °C for 1.5 h and then cooled to 18 °C, diluted with diethyl ether (100 mL), and washed with water (2 × 50 mL). The separated organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford azide **39** (60 mg, 81%) as a clear,

dx.doi.org/10.1021/jo400952u | J. Org. Chem. 2013, 78, 7100−7111

colorless oil, $[\alpha]_D$ +99 (*c* 1.2, $CHCl_3$) (R_f = 0.5 in 3:7 v/v ethyl acetate/hexane) [Found: $(M + H)^+$, 250.1555. $C_{13}H_{19}N_3O_2$ requires $(M + H)^+$, 250.1556]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.96 (dd, *J* = 5.7 and 9.9 Hz, 1H), 5.79 (dd, *J* = 3.6 and 9.9 Hz, 1H), 5.71 (d, *J* = 5.7 Hz, 1H), 4.64 (dd, *J* = 3.6 and 8.7 Hz, 1H), 4.51 (d, *J* = 8.7 Hz, 1H), 3.28 (t, *J* = 6.0 Hz, 2H), 2.25 (m, 2H), 1.60 (m, 4H), 1.39 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7 (C), 124.6 (CH), 122.8 (CH), 118.6 (CH), 105.3 (C), 73.3 (CH), 71.2 (CH), 51.3 (CH_2), 33.1 (CH_2), 28.6 (CH_2), 26.9 (CH_3), 25.1 (CH_3), 24.3 (CH_2). ν_{max} 2985, 2933, 2870, 2096, 1661, 1603, 1456, 1378, 1369, 1248, 1209, 1158, 1046, 1027, 870 cm^{-1}. Mass spectrum (EI, 70 eV) 249 ($M^{+\bullet}$, <1%), 206 (12), 162 (48), 134 (78), 121 (60), 107 (72), 91 (56), 79 (61), 70 (46), 56 (43), 43 (100).

Compound 40. A magnetically stirred solution of azide **39** (200 mg, 0.80 mmol) in benzene (40 mL) was heated at reflux for 72 h, cooled to 18 °C, and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to column chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) afforded, upon concentration of the appropriate fractions (R_f = 0.3 in 3:7 v/v ethyl acetate/hexane), a white solid. Recrystallization (diethyl ether/dichloromethane/hexane) of this material afforded triazoline **40** (180 mg, 90%) as a white, crystalline solid, mp 104−109 °C, $[\alpha]_D$ −436 (*c* 0.8, $CHCl_3$) [Found: $(M + H)^+$, 250.1554; C, 62.46; H, 7.53; N, 17.07. $C_{13}H_{19}N_3O_2$ requires $(M + H)^+$, 250.1556; C, 62.23; H, 7.68; N, 16.85%]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.69 (dm, *J* = 9.9 Hz, 1H), 5.58 (m, *J* = 9.9 Hz, 1H), 4.70 (d, *J* = 4.8 Hz, 1H), 4.67 (m, 1H), 4.51 (m, 1H), 4.28 (dd, *J* = 4.8 and 14.1 Hz, 1H), 3.28 (dt, *J* = 2.4 and 14.1 Hz, 1H), 1.82−1.41 (complex m, 6H), 1.39 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 127.9 (CH), 119.6 (CH), 109.6 (C), 79.2 (CH), 71.4 (CH), 69.7 (CH), 59.5 (C), 45.3 (CH_2), 28.1 (CH_3), 27.5 (CH_2), 26.9 (CH_3), 25.8 (CH_2), 18.5 (CH_2). ν_{max} 2978, 2926, 1608, 1478, 1444, 1379, 1368, 1326, 1301, 1222, 1194, 1158, 1100, 1047, 1025, 954, 914, 866, 845 cm^{-1}. Mass spectrum (EI, 70 eV) 249 ($M^{+\bullet}$, <1%), 206 (12), 164 (44), 134 (96), 121 (100), 55 (37), 43 (67).

Compound 41. Method A: A magnetically stirred solution of triazole **40** (79 mg, 0.32 mmol) in toluene (25 mL) was heated at reflux for 48 h, cooled to 18 °C, and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f = 0.1 in 3:7 v/v ethyl acetate/hexane) aziridine **41** (60 mg, 85%) as a clear, colorless oil, $[\alpha]_D$ +70 (*c* 0.8, $CHCl_3$) [Found: $M^{+\bullet}$, 221.1415. $C_{13}H_{19}NO_2$ requires $M^{+\bullet}$, 221.1416]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.96 (ddd, *J* = 1.2, 4.5, and 9.9 Hz, 1H), 5.37 (dd, *J* = 1.2 and 9.9 Hz, 1H), 4.40 (m, 2H), 3.21 (dt, *J* = 4.8 and 12.9 Hz, 1H), 2.64 (m, 1H), 2.01 (m, 3H), 1.45 (m, 2H) 1.26 (s, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 128.5 (CH), 126.3 (CH), 109.4 (C), 76.7 (CH), 72.8 (CH), 48.8 (CH_2), 39.8 (CH), 37.5 (C), 28.2 (CH_3), 26.4 (CH_3), 24.0 (CH_2), 21.1 (CH_2), 17.7 (CH_2). ν_{max} 2984, 2931, 2862, 1451, 1367, 1235, 1157, 1120, 1102, 1049, 953, 890, 872 cm^{-1}. Mass spectrum (EI, 70 eV) 221 ($M^{+\bullet}$, 5%), 206 (20), 164 (65), 149 (15), 134 (93), 121 (100), 93 (26), 69 (31), 57 (38), 55 (38), 43 (58).

Method B: A magnetically stirred solution of azide **39** (10 mg, 0.04 mmol) in toluene (2 mL) was heated at reflux for 72 h, cooled to 18 °C, and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) afforded, upon concentration of the appropriate fractions (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane), aziridine **41** (7 mg, 79%) as a clear, colorless oil. This material was identical, in all respects, with that obtained via Method A described immediately above.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data (CIFs), anisotropic displacement ellipsoid plots, and unit cell packing diagrams derived from the single-crystal analysis of compounds **15**, **23**, **34**, and **40**; ^{1}H and ^{13}C NMR spectra for compounds **10**−**16**, **18**−**28**, and **31**−**41**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Australian Research Council and the Institute of Advanced Studies for generous financial support.

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