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Variants of the Prins Cyclization for the Synthesis of Terpenoid Spiroethers and Oxabicyclo[3.3.1]Nonane Derivatives

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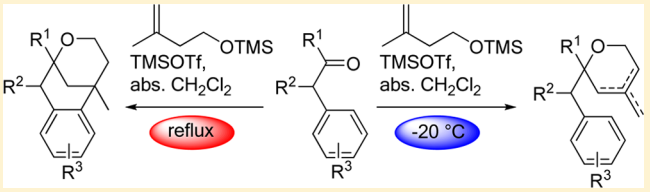
Supporting Information

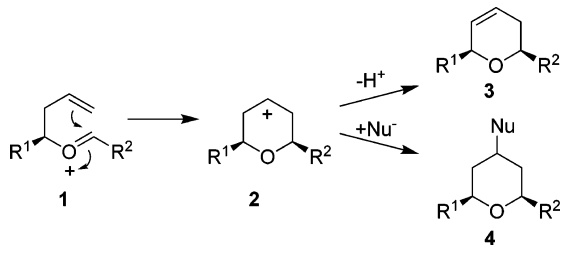
ABSTRACT: Terpenoid spiroethers are abundant natural flavors with significant impact, particularly in the food industry. We present in this article the synthesis of new derivatives of the well-known flavors theaspirane and vitispirane using a variant of the Prins cyclization starting from α,β-unsaturated or heterocyclic ketones. When aromatic ketones were used as the starting materials for Lewis acid-mediated cyclizations, an alternative pathway involving a domino sequence of Prins cyclization, followed by an intramolecular Friedel−Crafts alkylation, gave benzoannelated oxabicyclo[3.3.1]nonane derivatives. Different reaction pathways may be triggered by the reaction temperature to give with good selectivity either tetrahydropyran derivatives as conventional Prins products or oxabicyclo[3.3.1]nonane derivatives.



INTRODUCTION

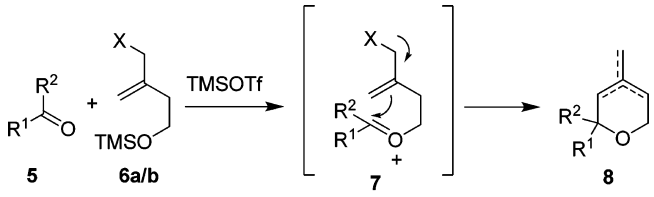
Prins reaction is the acid-mediated addition of an alkene to an aldehyde, and it is a fundamentally important method used for the construction of C−C bonds.[1,2] Various modifications are known, and a number of different carbonyl derivatives such as ketones, imines, acetals, esters, and orthoesters may be used as electrophiles instead of aldehydes. Different alkene nucleophiles such as allylsilanes (Sakurai variant)[3] and allylstannanes[4] may also be used in these conversions, and various Brønsted and Lewis acids are known to catalyze the reaction.[5,6] If the carbonyl component and the alkene (or alkyne) are appended, then a Prins cyclization to heterocycles will be the result (Scheme 1).[7−9]

Scheme 1. Prins-Type Cyclization and Subsequent Conversion of the Intermediate Carbocation



These cyclizations have been extensively used, particularly in natural products, for the synthesis of pyran derivatives.[10,11] The reaction mechanism is believed to involve cationic intermediates of type **2**.[12,13] Subsequent conversions of these cations allow the synthesis of structurally diverse products. If a proton (or another nucleofuge such as a trimethylsilyl group) is eliminated, then dihydropyran (**3**) is formed.[14−20] Alternatively, cation **2** may rearrange[21,22] or may be trapped by an internal or external nucleophile to give tetrahydropyran (**4**).[23−27] Many variants of these transformations have been developed and are now valuable concepts in natural products synthesis. Examples include Rychnovsky's segment coupling[28] and macrocyclization.[29−33] Marko and coworker have developed a one-pot method for the synthesis of pyran derivative **8** termed intramolecular silyl-modified Sakurai reaction (ISMS, Scheme 2).[34] This procedure allows the efficient synthesis of pyran

Scheme 2. Intramolecular Silyl-Modified Sakurai Reaction (ISMS) Developed by Marko



R^1, R^2 = alkyl; **6a**: X = H, **6b**: X = $SiMe_3$

derivative **8**, starting from a carbonyl derivative such as **5** and a silylether such as **6a** or **6b**. The regiochemistry of the resulting double bond in heterocycle **8** is dependent on the reaction temperature and the nature of the silyl ether **6a**/**b**.[35] At low temperature and using an allyl silane such as **6b** (X = $SiMe_3$), exocyclic methylene derivative **8** is obtained with good

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selectivity. This protocol is therefore particularly attractive for the synthesis of spirocyclic tetrahydropyrans with an *exo*-methylene group.[35,36] At higher temperature and using an allyl silylether like **6a** (X = H), dihydropyran **8** is the major product.

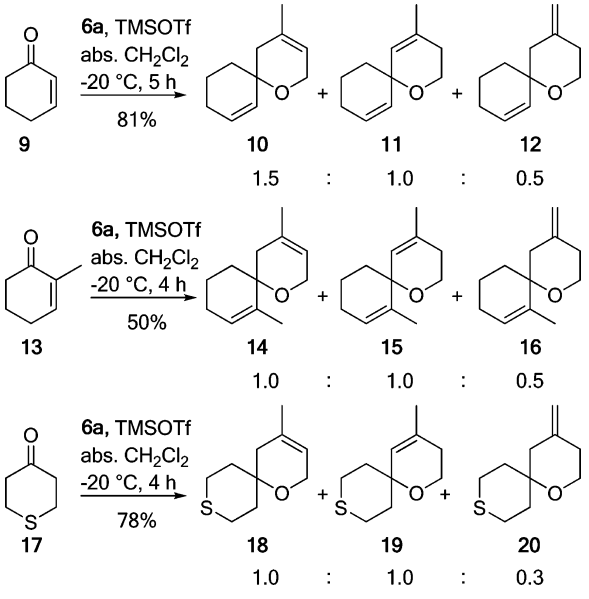
In this report, we describe the synthesis of novel spirocyclic terpenoids as structural analogues of important norisoprenoid flavors such as theaspirane and vitispirane via ISMS (a variant of Prins cyclization). In addition, a domino Prins/Friedel–Crafts sequence is described. This sequence allows the synthesis of benzoannelated oxabicyclo[3.3.1]nonane scaffolds, which are not easily synthesized by other methods.

RESULTS AND DISCUSSION

In the course of a project on biocatalytic oxidations of spirocyclic flavor compounds,[37] we became interested in methods for the synthesis of spirocyclic dihydropyrans with an endo double bond as analogues of norisoprenoid flavor compounds, such as theaspirane and vitispirane, that are important flavors in grapes and many other fruits.[38] The oxidative conversion of spirocyclic norisoprenoids by bacteria and fungi is a well-known process with an impact on the olfactory properties of plant extracts and is thus important in processes such as wine aging. We investigated these biocatalytic oxidations with regard to their potential in preparative chemistry, and we used the lyophilizate of edible fungus *Pleurotus sapidus* as a biocatalyst for allylic oxidation.[39] For these studies, we needed a set of spirocyclic dihydropyrans with endo double bonds of different electronic or steric properties and additional heteroatoms in the ring system.

Marko and co-worker have reported the exclusive formation of dihydropyran **8** with an endocyclic double bond if carbonyl compound **5** and a silylether such as **6a** (X = H) are treated with catalytic amounts of TMSOTf at low temperature.[36] We have thus subjected ketones **9**, **13**, and **17** to ISMS with silylether **6a** under the conditions reported by Marko (Scheme 3).

Scheme 3. ISMS of Cyclic Ketones 9, 13, and 17 with Silylether 6a[a]

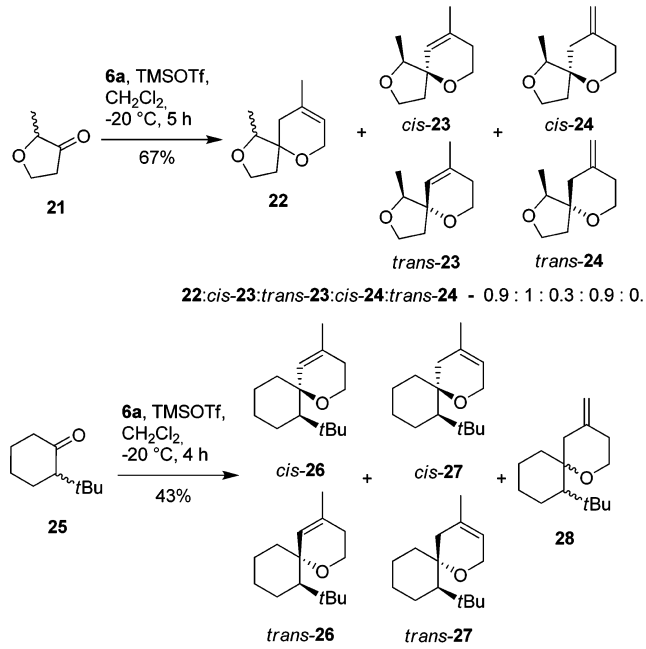


[a]Product distribution was measured by ^{1}H NMR analysis of the crude product.

The reactions proceeded with good overall yields, and each reaction gave two regioisomeric spirocyclic dihydropyrans with an endocyclic double bond as the major products along with a minor amount of the regioisomer with an exocyclic double bond. The formation of three regioisomers, usually an undesired outcome of ISMS, was ideal for our purpose because it allowed the synthesis of three unsaturated pyran derivatives, such as **10**–**12**, from a single ketone. Most of the spirocompounds obtained by this route were successfully separated by column chromatography.

Next, we used α-substituted racemic ketones **21** and **25** as starting materials to obtain a mixture of regio- and stereoisomeric spirocompounds, respectively. In each case, we have been able to separate most isomers by column chromatography. As shown in Scheme 4, the products obtained have low stereoselectivity.

Scheme 4. ISMS with α-Substituted Ketones 21 and 25[a]



[a]For pure diastereoisomers, the relative configuration is given. Only one enantiomer of racemic compounds is shown. The product distribution was measured by ^{1}H NMR analysis of the crude product.

The conversion of α-phenyl-substituted cyclohexanone **29** was also successful, giving a mixture of regio- and stereoisomeric spirocyclic compounds **30** and **31** (Scheme 5). However, in this case we noted an additional product in the ^{1}H NMR spectra of the crude product that lacked the characteristic olefinic protons of the expected products of ISMS.

The unexpected product was identified as oxabicyclo[3.3.1]-nonane derivative (*1R*,8R*,13S**)-**32** by both NMR and HRMS analysis. ISMS products *cis*-**30** and *trans*-**31** were obtained as colorless oils, whereas *trans*-**30** and (*1R*,8R*,13S**)-**32** were obtained as colorless solids that gave suitable crystals for X-ray analysis upon crystallization from pentane. The crystal structure of (*1R*,8R*,13S**)-**32** is depicted in Figure 1. It confirms our analysis by NMR, particularly with respect to the cis arrangement of the phenyl

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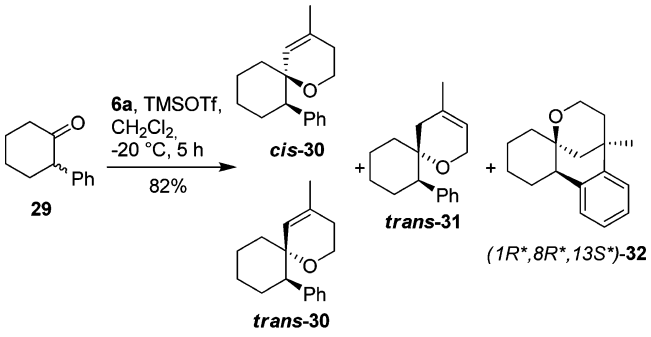
Scheme 5. ISMS of α-Phenylcyclohexanone (29)[a]



[a]Only one enantiomer of racemic compounds is shown. The product distribution was measured by the ^{1}H NMR analysis of the crude product.

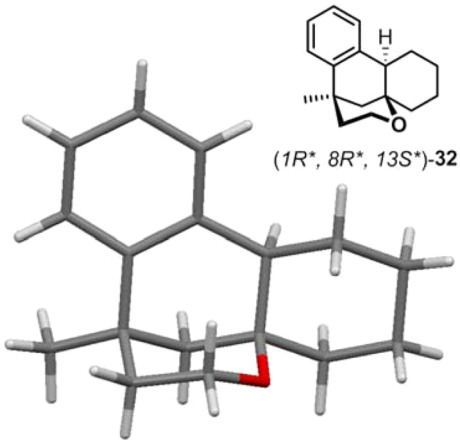


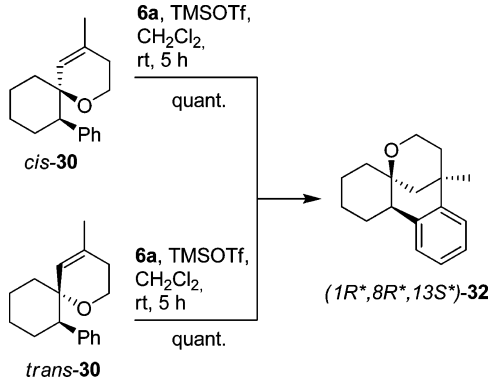
Figure 1. X-ray structure of oxabicyclononane-derivative (1*R**,8*R**,13*S**)-**32**.

ring and the ether bridge at the "eastern"-cyclohexyl ring. To the best of our knowledge, similar cyclization products have not been reported previously for either Prins- or Sakurai-type cyclizations.

If the reaction is performed at room temperature in CH_2Cl_2, then oxabicyclononane derivative (1*R**,8*R**,13*S**)-**32** is the major product (Scheme 6). The formation of (1*R**,8*R**,13*S**)-**32** as a single diastereoisomer may be rationalized by the initial Prins-type cylization of intermediate **33** to diastereomeric cations *cis*-**34** and *trans*-**34**. These cations might then eliminate a proton to give spirocyclic products **30** and **31**. Alternatively, a subsequent intramolecular Friedel–Crafts alkylation of **34** gives (1*R**,8*R**,13*S**)-**32**. Cation *trans*-**34** is unable to undergo Friedel–Crafts cyclization to oxabicyclononane (1*R**,8*R**,13*S**)-**32** and can form only spiroether *trans*-**30** or *trans*-**31** upon elimination of a proton. However, if the reaction is performed at room temperature, spiroethers **30** and **31** are observed only in the NMR analysis as minor compounds in the crude product. Consequently, the whole process seems to be under thermodynamic control.

We have tested this hypothesis with the conversion of diastereomeric spiroethers *cis*-**30** and *trans*-**30**. As depicted in Scheme 7, we obtained in both cases the identical product,

Scheme 7. Intramolecular Friedel–Crafts Alkylation of Diastereomeric Spiroethers *cis*-30 and *trans*-30[a]

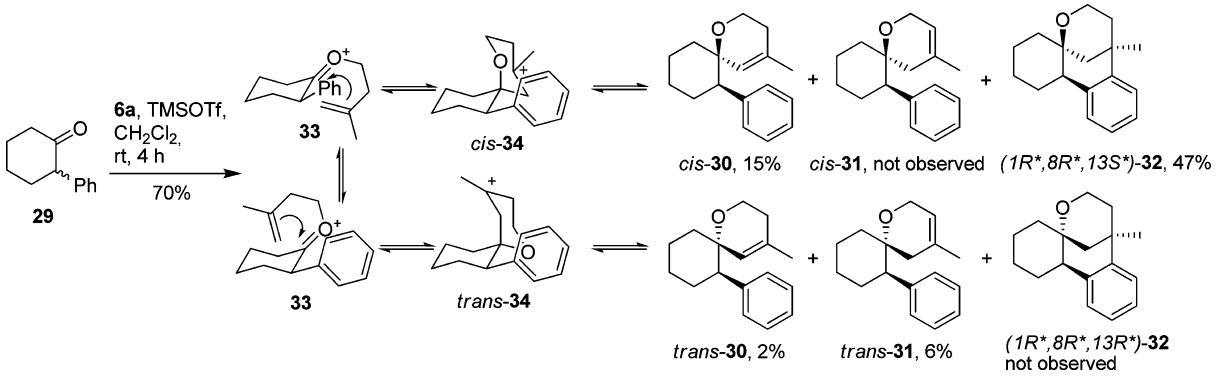


[a]Only one enantiomer of racemic compounds is shown.

(1*R**,8*R**,13*S**)-**32** as a single diastereoisomer, indicating the reversible formation of cationic intermediates **33** and **34**. Examples of domino Prins/Friedel–Crafts reactions are quite rare. Only a small number of inter- and intramolecular variants have been described.[27,40−45]

In addition to phenylcyclohexanone **29**, we have also used phenylacetone derivatives **35a**–**35e** as the starting materials for the evaluation of the domino-cyclization pathway. The results are depicted in Table 1. Tetrahydropyrans **36**–**38** were obtained in each case at low temperature (Table 1, entries 1, 4, 7, and 11). Only meta-substituted phenylacetone **35b** gave

Scheme 6. Reaction of Cyclic Ketone 29 with Silylether 6a[a]



[a]For pure diastereomers, the relative configuration and isolated yields are given. Only one enantiomer of racemic compounds is shown.

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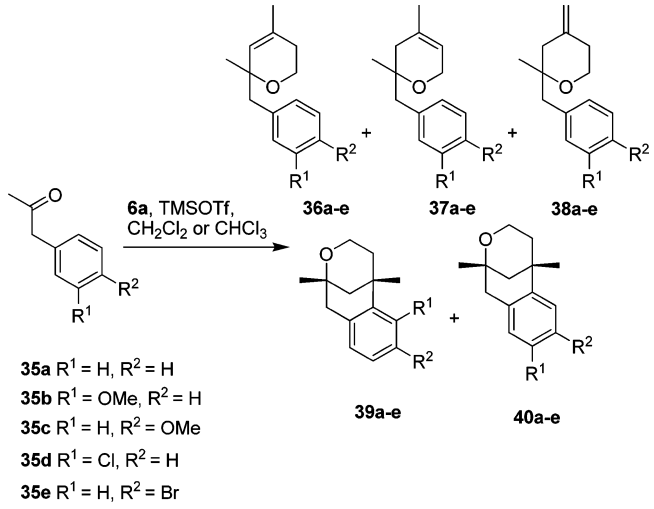
Table 1. Domino Prins/Friedel–Crafts Conversion of Phenylacetone Derivatives 35a–35e

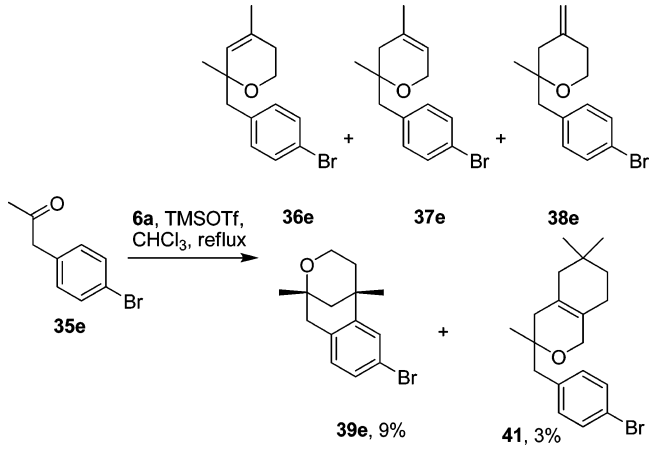


entry	substrate	temperature	R^1	R^2	36/37/38/39/40[a]	yield of 39 or 40
1	**35a**	−20 °C	H	H	48:24:28:0[b]	
2	**35a**	rt	H	H	42:26:0:32[b]	
3	**35a**	reflux[c]	H	H	15:11:0:74[b]	53% (**39a**)
4	**35b**	−20 °C	OMe	H	30:30:10:12:18	
5	**35b**	rt	OMe	H	14:14:0:26:46	
6	**35b**	reflux[c]	OMe	H	0:0:0:39:61	34% (**39b**), 51% (**40b**)
7	**35c**	−20 °C	H	OMe	56:28:16:0[b]	
8	**35c**	rt	H	OMe	32:24:0:44[b]	
9	**35c**	reflux[c]	H	OMe	0:0:0:100[b]	83% (**39c**)
10	**35d**	reflux[d]	Cl	H	16:9:0:0:75	41% (**40d**)
11	**35e**	−10 °C	H	Br	55:36:9:0[b]	
12	**35e**	rt	H	Br	59:41:0:0[b]	
13	**35e**	reflux[c]	H	Br	51:35:0:14[b]	

[a]Product distribution was measured by ^{1}H NMR analysis of the crude products. [b]Four isomers are possible; **39** and **40** are identical. [c]The reaction was performed in CH_2Cl_2. [d]The reaction was performed in $CHCl_3$.

the two regioisomeric domino products **39b** and **40b**, observed in the ^{1}H NMR analysis as small components of the crude product mixture (Table 1, entry 4). At room temperature, we obtained mixtures of all possible isomers for electron-rich phenylacetone derivatives **35a–c** (Table 1, entries 2, 5, and 8), whereas at reflux in CH_2Cl_2 domino products **39** and **40** were predominant (Table 1, entries 3, 6, and 9). All products were obtained as colorless oils except for domino product **39b** that was obtained as a colorless solid giving, upon crystallization from pentane, suitable crystals for X-ray analysis (Supporting Information). As expected for Friedel–Crafts-type reactions, the formation of domino products **39** and **40** was dependent on the electronic effects of additional substituents on the aromatic system. Consequently, halogenated aromatics **35d** and **35e** are less-reactive substrates for domino cyclizations to oxabicyclononanes **39** and **40**. With 3-chlorophenylacetone **35d** as a starting material, a reasonable yield of 41% for oxabicyclononane **40d** (Table 1, entry 10) can be achieved at higher temperatures (reflux in $CHCl_3$) and the addition of 0.4 equiv of TMSOTf instead of 0.2 equiv of TMSOTf (as used in all other cases). For strongly deactivated substrate 4-bromophenylacetone **35e** (with bromine in meta position relative to the site of alkylation), domino product **39e** is only a minor component of the reaction mixture when in refluxing CH_2Cl_2 (Table 1, entry 13). Even at reflux in $CHCl_3$ and with additional TMSOTf, domino product **39e** was isolated only in small quantities (Scheme 8). It should be noted that alternative reaction

Scheme 8. Product Distribution for the Conversion of 4-Bromophenylacetone (35e) with 6a at Elevated Temperature[a]



[a]Only one enantiomer of the racemic compounds is shown.

pathways become increasingly important at high reaction temperatures, eventually leading to complex product mixtures. This is shown in Scheme 8 for the conversion of 4-bromophenylacetone **35e** to tetrahydropyrans **36e–38e**, oxabicyclononane **39e**, and new bicyclic product **41**. The latter

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two compounds have been isolated in pure form from the rather complex crude reaction mixture. Domino products **39** and **40** were obtained as racemic mixtures. However, most derivatives may be separated by SFC on commercially available chiral stationary phases (Supporting Information) according to established protocols.[46]

CONCLUSIONS

TMSOTf-mediated ISMS is an attractive method for the assembly of substituted di- and tetrahydropyrans from various carbonyl compounds and silylethers. Prins-type cyclization proceeds via a cationic intermediate, which may either eliminate a proton (or another nucleofuge) or be trapped with a suitable nucleophile to give pyran derivatives. We have used a variant of ISMS for the preparation of spirocyclic ethers that are similar to norisoprenoid flavor compounds such as theaspirane and vitispirane. If ketones with aromatic side chains were used as the starting materials, then an alternative reaction pathway was observed, and the intermediate cation was trapped by an intramolecular Friedel–Crafts reaction. This rare example of an intramolecular Prins/Friedel–Crafts domino cyclization gave benzoannelated oxabicyclononane derivatives **32**, **39**, and **40** with good selectivity. For substrates bearing electron-rich aromatic substituents, the reaction proceeds under thermodynamic control at reflux in CH_2Cl_2 to give oxabicyclononane derivatives **32**, **39**, and **40** in good yields. As expected in Friedel–Crafts-type conversions, the formation of oxabicyclononanes is sensitive to the electronic factors of additional substituents on the participating aromatic ring. With substrates bearing deactivating substituents, more drastic reaction conditions (reflux in $CHCl_3$ and 0.4 equiv of TMSOTf) are required to achieve conversion to the domino products, resulting in more complex crude product mixtures.

EXPERIMENTAL SECTION

General Methods. TLC was performed on silica gel–aluminum sheets. The reagent used for developing TLC plates was phosphomolybdic acid (5 g of phosphomolybdic acid in 100 mL of EtOH). Flash-column chromatography was performed on silica gel (40–60 μm). Compounds **10**, **11**, and **12** were prepared as described previously.[47]

^{1}H NMR chemical shifts were referenced to the residual nondeuterated solvent signal ($CDCl_3$, δ_H = 7.26 ppm). ^{13}C NMR chemical shifts were referenced to the solvent signal ($CDCl_3$, δ = 77.16 ppm). The coupling constant (J) is given in hertz. The chemical shifts (δ) are reported in ppm, and the signal patterns are indicated as s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), m (multiplet), and br (broad). NMR signals have been assigned on the basis of 2D NMR (HH-COSY, HMBC, and HSQC) experiments. Relative stereochemistry has been assigned on the basis of 1D or 2D NOE experiments. The atom numbers used for NMR peak assignment do not refer to IUPAC nomenclature and are available from the structures provided with the NMR spectra in the Supporting Information. ESI and APCI mass spectra were recorded in positive mode on an ESI-TOF instrument. Samples were dissolved in either CH_3CN–H_2O mixtures or pure MeOH and directly injected by using a syringe. All of the reagents were reagent grade and used without further purification unless otherwise specified. Solvents for the reactions were distilled prior to use. All air- or moisture-sensitive reactions were conducted under a nitrogen or argon atmosphere in flame- or oven-dried glassware. Absolute CH_2Cl_2 was distilled from CaH_2.

*Spiroethers **14–16**.* In a flame-dried round-bottomed flask, 2-methyl-2-cyclohexenone **13** (1.02 mL, 9 mmol) and TMS-ether **6a** (1.78 mL, 9 mmol) were dissolved in absolute CH_2Cl_2 (20 mL) at −20 °C and stirred for 5 min under N_2. TMSOTf (326 μL, 1.8 mmol) was added, and the resulting mixture was stirred at −20 °C for 4 h. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting bright-yellow oil was purified by column chromatography (pentane/Et_2O, 96:4) to give spiroethers **14** (300 mg, 1.7 mmol, 19%) and **15** (290 mg, 1.6 mmol, 18%) as colorless oils. In addition, a mixture of isomers **14** and **16** (215 mg, 1.2 mmol, 13%) was obtained.

4,7-Dimethyl-1-oxaspiro[5.5]-undeca-3,7-diene (**14**): R_f: 0.32 (pentane/Et_2O, 96:4; phosphomolybdic acid). HRMS (ESI): calculated for $C_{12}H_{18}O + Na^+$ = 201.1250, found = 201.1251. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55 (s, 1H, 8H), 5.40 (s, 1H, 3H), 4.22–4.14 (m, 1H, 2H), 4.13–4.06 (m, 1H, 2H), 2.35 (d, $^2J_{H,H}$ = 17.4 Hz, 1H, 5H), 2.09–1.91 (m, 2H, 9H), 1.89–1.83 (m, 1H, 11H), 1.74–1.64 (m, 9H, 5H/10H/11H/12H/13H), 1.56–1.47 (m, 1H, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.3 (C7), 131.0 (C4), 126.2 (C8), 118.7 (C3), 72.5 (C6), 60.9 (C2), 35.8 (C5), 30.9 (C11), 25.8 (C9), 23.7 (C12), 20.0 (C10), 18.0 (C13). IR (thin film): ν = 2970, 2929, 2833, 1444, 1379, 1113, 1009, 985, 803 cm^{-1}.

4,7-Dimethyl-1-oxaspiro[5.5]-undeca-4,7-diene **15**: R_f: 0.24 (pentane/Et_2O, 96:4; phosphomolybdic acid). HRMS (APCI): calculated for $C_{12}H_{18}O + H^+$ = 179.1413, found = 179.1436. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.60–5.57 (m, 1H, 8H), 5.19 (s, 1H, 5H), 3.82 (ddd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 6.0 Hz, $^3J_{H,H}$ = 1.5 Hz, 1H, 2H), 3.71 (ddd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 11.2 Hz, $^3J_{H,H}$ = 3.3 Hz, 1H, 2H), 2.27–2.17 (m, 1H, 3H), 2.06–1.98 (m, 1H, 9H), 1.95–1.86 (m, 2H, 9H/11H), 1.72 (s, 3H, 12H), 1.71–1.65 (m, 2H, 3H/10H), 1.60–1.58 (m, 3H, 13H), 1.57–1.52 (m, 1H, 10H), 1.50–1.43 (m, 1H, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.7 (C7), 132.5 (C4), 127.3 (C5), 126.3 (C8), 73.6 (C6), 59.5 (C2), 33.3 (C11), 30.0 (C3), 25.8 (C9), 23.5 (C12), 18.8 (C10), 18.6 (C13). IR (thin film): ν = 2968, 2930, 2859, 2834, 1438, 1267, 1194, 1087, 981, 893, 807, 760 cm^{-1}.

*Spiroethers **18–20**.* In a flame-dried round-bottomed flask, tetrahydro-4*H*-thiopyran-4-one **17** (1.16 g, 10 mmol) and TMS-ether **6a** (1.58 g, 10 mmol) were dissolved in absolute CH_2Cl_2 (20 mL) at −20 °C and stirred for 5 min under N_2. TMSOTf (362 μL, 2 mmol) was added, and the resulting mixture was stirred at −20 °C for 4 h. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting bright-yellow oil was purified by column chromatography (pentane/Et_2O, 20:1 → 9:1) to give a mixture of spiroethers **18**, **19**, and **20** (1.43 g, 7.8 mmol, 78%) in a ratio of 1:1:0.3, respectively. Repeated column chromatography gave analytical probe **19** a as colorless oil.

4-Methyl-1-oxa-9-thiaspiro[5.5]undec-4-ene (**19**): R_f: 0.66 (pentane/Et_2O, 9:1; phosphomolybdic acid). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.23–5.22 (m, 1H, 5H), 3.70 (t, $^3J_{H,H}$ = 5.5 Hz, 2H, 2H), 2.99–2.92 (m, 2H, 8H), 2.34–2.29 (m, 2H, 8H), 1.95–1.91 (m, 4H, 7H/3H), 1.66 (s, 3H, 9H), 1.64–1.58 (m, 2H, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.7 (C4), 128.2 (C5), 70.4 (C6), 58.6 (C2), 36.3 (C7), 30.0 (C3), 23.7 (C8), 23.3 (C9). IR (thin film): ν = 2930, 2905, 2822, 1424, 1273, 1147, 1105, 1089, 779 cm^{-1}.

*Spiroethers **22–24**.* In a flame-dried round-bottomed flask, *rac*-2-methyltetrahydro-4-furanone **21** (1.00 g, 10 mmol) and TMS-ether **6a** (1.58 g, 10 mmol) were dissolved in absolute CH_2Cl_2 (20 mL) at −20 °C and stirred for 5 min under N_2. TMSOTf (362 μL, 2 mmol) was added, and the resulting mixture was stirred at −20 °C for 5 h under N_2. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting bright-yellow oil was purified by column chromatography (pentane/Et_2O, 15:1 → 7:4) to give a mixture of all isomers (1.12 g, 6.7 mmol, 67%). Repeated column chromatography gave isolated spiroethers *cis*-**23** (185 mg, 1.1 mmol, 11%) and *cis*-**24** (118 mg, 0.7 mmol, 7%) as colorless oils.

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(1*S**,5*S**)-1,9-Dimethyl-2,6-dioxaspiro[4.5]dec-9-ene (*cis*-**23**): R_f: 0.43 (pentane/Et_2O, 1:1; phosphomolybdic acid). HRMS (APCI): calculated for $2C_{10}H_{16}O_2 + H^+$ = 337.2373, found = 337.2375. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.16 (s, 1H, 10H), 3.97 (q, $^3J_{H,H}$ = 8.0 Hz, 1H, 3H), 3.90−3.85 (m, 1H, 7H), 3.83−3.78 (m, 1H, 3H), 3.66−3.57 (m, 2H, 1H/7H), 2.21−2.13 (m, 1H, 8H), 2.10−2.04 (m, 1H, 4H), 1.91−1.83 (m, 1H, 4H), 1.75 (br s, 1H, 8H), 1.70 (s, 3H, 11H), 1.11 (d, $^3J_{H,H}$ = 6.3 Hz, 3H, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.0 (C9), 122.7 (C10), 82.3 (C1), 81.7 (C5), 65.9 (C3), 60.5 (C7), 37.9 (C4), 30.0 (C8), 23.4 (C11), 13.1 (C12). IR (thin film): ν = 2980, 2883, 1731, 1369, 1238, 1065, 876 cm^{-1}.

(1*S**,5*S**)-1-Methyl-9-methylene-2,6-dioxaspiro[4.5]decane (*cis*-**24**): R_f: 0.54 (pentane/Et_2O, 1:1; phosphomolybdic acid). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.77 (q, $^4J_{H,H}$ = 1.7 Hz, 1H, 11H), 4.74 (q, $^4J_{H,H}$ = 1.7 Hz, 1H, 11H), 3.99−3.86 (m, 1H, 3H), 3.91−3.86 (m, 1H, 7H), 3.74−3.68 (m, 1H, 3H), 3.58−3.50 (m, 2H, 1H/7H), 2.30−2.22 (m, 2H, 8H/10H), 2.16−2.08 (m, 2H, 4H/8H), 2.03−2.00 (m, 1H, 10H), 1.79−1.73 (m, 1H, 4H), 1.22 (d, $^3J_{H,H}$ = 6.3 Hz, 3H, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1 (C9), 109.6 (C11), 83.2 (C5), 82.4 (C1), 65.6 (C3), 63.7 (C7), 42.0 (C10), 35.1 (C8), 33.7 (C4), 13.5 (C12). IR (thin film): ν = 2980, 2889, 1735, 1368, 1237, 1176, 1076, 1039, 976 cm^{-1}. GC−MS *m*/*z* 168 (M^+, 100), 124 (82), 109 (51), 95 (33), 79 (26), 67 (94), 53 (32), 43 (54).

Spiroethers ***26*****−*****28***. In a flame-dried round-bottomed flask, *rac*-1-*tert*-butylcyclohexanone **25** (2.58 mL, 15 mmol) and TMS-ether **6a** (2.96 mL, 15 mmol) were dissolved in absolute CH_2Cl_2 (50 mL) at −20 °C and stirred for 5 min under N_2. TMSOTf (550 μL, 3 mmol) was added, and the resulting mixture was stirred at −20 °C for 4 h. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (30 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting bright-yellow oil was purified by column chromatography (pentane/CH_2Cl_2, 100:1 → 7:3) to give a mixture of isomers *cis*-**26**, *trans*-**26**, *cis*-**27**, and *trans*-**27** (1.43 g, 6.4 mmol, 43%). Repeated column chromatography gave pure spiroethers *cis*-**26** (192 mg, 0.9 mmol, 6%), *trans*-**26** (283 mg, 1.3 mmol, 9%), *cis*-**27** (92 mg, 0.4 mmol, 3%), and *trans*-**27** (137 mg, 0.6 mmol, 4%) as colorless oils.

(6*S**,7*R**)-7-*tert*-Butyl-4-methyl-1-oxaspiro[5.5]undec-4-ene (*cis*-**26**): R_f: 0.32 (pentane/CH_2Cl_2, 100:1; phosphomolybdic acid). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.31 (s, 1H, 5H), 3.79 (dd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 6.5 Hz, 1H, 2H), 3.67 (dt, $^3J_{H,H}$ = 11.5 Hz, $^2J_{H,H}$ = 3.5 Hz, 1H, 2H), 2.21−2.16 (m, 1H, 3H), 1.90−1.86 (m, 1H, 11H), 1.75−1.72 (m, 1H, 9H), 1.67−1.57 (m, 3H, 3H/8H/8H), 1.64 (s, 3H, 12H), 1.48 (tt, $^3J_{H,H}$ = 3.8 Hz, $^3J_{H,H}$ = 13.3 Hz, 1H, 10H), 1.37−1.34 (m, 1H, 10H), 1.21−1.13 (m, 2H, 7H/9H), 1.04 (dt, $^3J_{H,H}$ = 13.9 Hz, $^2J_{H,H}$ = 3.9 Hz, 1H, 11H), 0.93 (s, 9H, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.9 (C5), 126.4 (C4), 76.2 (C6), 58.3 (C2), 55.0 (C7), 36.0 (C11), 34.9 (C13), 30.9 (C14), 29.6 (C3), 27.2 (C9), 23.8 (C8), 23.4 (C12), 21.4 (C10). IR (thin film): ν = 2954, 2929, 2913, 2854, 1444, 1363, 1269, 1235, 1085, 872, 765 cm^{-1}. GC−MS *m*/*z* 222 (M^+, 20), 207 (43), 179 (28), 165 (35), 151 (22), 123 (100).

(6*R**,7*R**)-7-*tert*-Butyl-4-methyl-1-oxaspiro[5.5]undec-4-ene (*trans*-**26**): R_f: 0.14 (pentane/CH_2Cl_2, 100:1; phosphomolybdic acid). HRMS (ESI): calculated for $C_{15}H_{26}O + Na^+$ = 245.1881, found = 245.1883. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.74 (s, 1H, 5H), 3.87 (dt, $^3J_{H,H}$ = 11.5 Hz, $^2J_{H,H}$ = 3.7 Hz, 1H, 2H), 3.78 (dd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 6.4 Hz, 1H, 2H), 2.32−2.26 (m, 1H, 3H), 2.14−2.11 (m, 1H, 11H), 1.81−1.78 (m, 1H, 8H), 1.78−1.75 (m, 1H, 9H), 1.70 (s, 3H, 12H), 1.64 (dd, $^2J_{H,H}$ = 3.6 Hz, $^3J_{H,H}$ = 17.0 Hz, 1H, 3H), 1.62−1.59 (m, 1H, 10H), 1.36−1.31 (m, 2H, 7H/8H), 1.30−1.23 (m, 3H, 9H, 10H, 11H), 0.91 (s, 9H, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.9 (C5), 124.5 (C4), 77.0 (C6), 58.1 (C2), 55.0 (C7), 40.5 (C11), 34.5 (C13), 30.4 (C14), 29.9 (C3), 27.4 (C9), 26.0 (C8), 23.9 (C12), 23.8 (C10). IR (thin film): ν = 2929, 2861, 1448, 1364, 1102, 1070, 889 cm^{-1}.

(6*S**,7*R**)-7-*tert*-Butyl-4-methyl-1-oxaspiro[5.5]undec-3-ene (*cis*-**27**): R_f: 0.44 (pentane/CH_2Cl_2, 100:1; phosphomolybdic acid). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.37 (s, 1H, 3H), 4.07−3.99 (m, 2H, 2H), 2.77 (d, $^2J_{H,H}$ = 17.0 Hz, 1H, 5H), 2.08 (td, $^2J_{H,H}$ = 13.9 Hz, $^3J_{H,H}$ = 4.0 Hz, 1H, 11H), 1.74−1.61 (2m, 3H, 8H/8H/9H), 1.67 (s, 3H, 12H), 1.53 (d, $^2J_{H,H}$ = 17.0 Hz, 1H, 5H), 1.47−1.42 (m, 1H, 10H), 1.40−1.35 (m, 1H, 10H), 1.27−1.23 (m, 2H, 7H/9H), 1.11−1.06 (m, 1H, 11H), 1.04 (s, 9H, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.8 (C4), 118.7 (C3), 75.8 (C6), 60.0 (C2), 53.7 (C7), 39.4 (C5), 34.7 (C13), 33.5 (C11), 31.8 (C14), 26.5 (C9), 24.6 (C8), 23.8 (C12), 21.9 (C10). IR (thin film): ν = 2932, 2867, 1716, 1689, 1446, 1366, 1125, 949 cm^{-1}. GC−MS *m*/*z* 180 (35), 137 (100), 135 (62), 124 (35), 82 (69).

(6*R**,7*R**)-7-*tert*-Butyl-4-methyl-1-oxaspiro[5.5]undec-3-ene (*trans*-**27**): R_f: 0.18 (pentane/CH_2Cl_2, 100:1; phosphomolybdic acid). HRMS (APCI): calculated for $C_{15}H_{26}O-H_2O + H^+$ = 205.1956, found = 205.1948; for $C_{15}H_{26}O + H^+$ = 223.2062, found = 223.2048. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.36 (s, 1H, 3H), 4.18−4.13 (m, 1H, 2H), 4.06−4.01 (m, 1H, 2H), 2.43 (d, $^2J_{H,H}$ = 17.0 Hz, 1H, 5H), 2.16−2.13 (m, 1H, 11H), 1.86 (dd, $^2J_{H,H}$ = 17.1 Hz, $^4J_{H,H}$ = 2.5 Hz, 1H, 5H), 1.76−1.71 (m, 2H, 8H/9H), 1.70 (s, 3H, 12H), 1.64−1.61 (m, 1H, 10H), 1.36−1.34 (m, 1H, 7H), 1.23−1.19 (m, 3H, 8H/9H/10H), 1.11−1.05 (m, 1H, 11H), 1.01 (s, 9H, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.2 (C4), 118.9 (C3), 76.5 (C6), 59.8 (C2), 54.8 (C7), 34.8 (C11), 34.4 (C13), 31.1 (C14), 30.3 (C5), 27.3 (C9), 26.5 (C8), 24.3 (C10), 23.9 (C12).

Spiroethers ***30*** *and* ***31*** *and Oxabicyclononane (1R*,8R*,13S*)-***32***.* In a flame-dried round-bottomed flask, *rac*-2-phenylcyclohexanone **29** (2.614 g, 15 mmol) and TMS-ether **6a** (2.96 mL, 15 mmol) were dissolved in absolute CH_2Cl_2 (40 mL) at −20 °C and stirred for 5 min under N_2. TMSOTf (550 μL, 3 mmol) was added, and the resulting mixture was stirred at −20 °C for 4 h. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (30 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting bright-yellow oil was purified by column chromatography (pentane/CH_2Cl_2, 100:1 → 0:1) to give a mixture of isomers *trans*-**30**, *cis*-**30**, *trans*-**31**, and (1*R**,8*R**,13*S**)-**32** (2.98 g, 12.3 mmol, 82%). Repeated column chromatography gave isolated spiroether *trans*-**30** (180 mg, 0.7 mmol, 5%) as colorless crystals, *trans*-**31** (780 mg, 3.2 mmol, 21%) and *cis*-**30** (570 mg, 2.4 mmol, 16%) as colorless oils, and oxabicyclononane derivative (1*R**, 8*R**, 13*S**)-**32** (380 mg, 1.6 mmol, 10%) as colorless crystals.

(6*S**,7*R**)-4-Methyl-7-phenyl-1-oxaspiro[5.5]undec-4-ene (*cis*-**30**): R_f: 0.39 (pentane/CH_2Cl_2, 8:2; phosphomolybdic acid). HRMS (ESI): calculated for $C_{17}H_{22}O + Na^+$ = 265.1568, found = 265.1566. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.18−7.16 (m, 2H, Ph), 7.11−7.02 (m, 3H, Ph), 5.05 (s, 1H, 5H), 3.62 (ddd, $^2J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 5.6 Hz, $^3J_{H,H}$ = 1.7 Hz, 1H, 2H), 3.50 (dt, $^2J_{H,H}$ = 11.0 Hz, $^2J_{H,H}$ = 3.5 Hz, 1H, 2H), 2.40 (dd, $^3J_{H,H}$ = 13.0 Hz, $^3J_{H,H}$ = 3.4 Hz, 1H, 7H), 2.04 (dq, $^3J_{H,H}$ = 13.0 Hz, $^3J_{H,H}$ = 3.7 Hz, 1H, 8H), 1.90−1.87 (m, 1H, 11H), 1.77−1.70 (m, 1H, 9H), 1.63 (tt, $^3J_{H,H}$ = 13.2 Hz, $^3J_{H,H}$ = 3.8 Hz, 1H, 10H), 1.54−1.42 (m, 3H, 3H/8H/10H), 1.35 (s, 3H, 12H), 1.33−1.32 (m, 1H, 3H), 1.26 (tt, $^3J_{H,H}$ = 13.2 Hz, $^3J_{H,H}$ = 3.8 Hz, 1H, 9H), 1.18 (dt, $^3J_{H,H}$ = 13.7 Hz, $^2J_{H,H}$ = 4.0 Hz, 1H, 11H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1 (C13), 131.8 (C4), 129.6 (C14), 128.6 (C5), 127.0 (C15), 125.7 (C16), 74.6 (C6), 59.4 (C2), 53.4 (C7), 34.9 (C11), 29.9 (C3), 28.4 (C8), 26.5 (C9), 23.1 (C12), 21.3 (C10). IR (thin film): ν = 2927, 2856, 1445, 1105, 1085, 758, 698 cm^{-1}.

(6*R**,7*R**)-4-Methyl-7-phenyl-1-oxaspiro[5.5]undec-3-ene (*trans*-**31**): R_f: 0.49 (pentane/CH_2Cl_2, 8:2; phosphomolybdic acid). HRMS (ESI): calculated for $C_{17}H_{22}O + Na^+$ = 265.1568, found = 265.1568. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, $^3J_{H,H}$ = 7.4 Hz, 2H, 14H), 7.28 (t, $^3J_{H,H}$ = 7.5 Hz, 2H, 15H), 7.21 (t, $_3J_{H,H}$ = 7.4 Hz, 1H, 16H), 5.30 (s, 1H, 3H), 4.11 (s, 2H, 2H), 2.54 (dd, $^3J_{H,H}$ = 12.8 Hz, $^3J_{H,H}$ = 3.6 Hz, 1H, 7H), 2.34−2.29 (m, 1H, 11H), 2.20 (dq, $^3J_{H,H}$ = 12.8 Hz, $^2J_{H,H}$ = 4.0 Hz, 1H, 8H), 2.04 (d, $^3J_{H,H}$ = 17.4 Hz, 1H, 5H), 1.88−1.83 (m, 1H, 9H), 1.70−1.60 (m, 3H, 8H/10H/10H), 1.59 (s, 3H, 12H), 1.44 (tt, $^3J_{H,H}$ = 13.0 Hz, $^3J_{H,H}$ = 4.0 Hz, 1H, 9H), 1.37 (d, $^2J_{H,H}$ = 17.1 Hz, 1H, 5H), 1.07 (dt, $^3J_{H,H}$ = 13.8 Hz, $^2J_{H,H}$ = 4.1 Hz, 1H, 11H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0 (C13), 130.5 (C4), 130.0 (C14),

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127.8 (C15), 126.1 (C16), 118.3 (C3), 72.5 (C6), 60.3 (C2), 53.7 (C7), 38.2 (C5), 32.2 (C11), 29.9 (C8), 27.1 (C9), 23.5 (C12), 21.8 (C10). IR (thin film): ν = 2974, 2931, 2856, 1715, 1685, 1445, 1381, 1120, 1031, 994, 969, 761, 700 cm^{-1}.

(6*R**,7*R**)-4-Methyl-7-phenyl-1-oxaspiro[5.5]undec-4-ene (*trans*-**30**): R_f: 0.24 (pentane/CH_2Cl_2, 6:4; phosphomolybdic acid). Mp: 47.1−50.0 °C. HRMS (ESI): calculated for $C_{17}H_{22}O$ + Na^+ = 265.1568, found = 265.1580; for $2C_{17}H_{22}O$ + Na^+ = 507.3239, found = 507.3245. Elemental anal. calculated for $C_{17}H_{22}O$: C, 84.25%; H, 9.15%; O, 6.60%; found: C, 84.00%; H, 9.05%; O, 6.85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23−7.14 (m, 5H, 14H/15H/16H), 5.84−5.81 (m, 1H, 5H), 3.60 (ddd, $^2J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 4.1 Hz, 1H, 2H), 3.27 (td, $^2J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 4.7 Hz, 1H, 2H), 2.76 (dd, $^3J_{H,H}$ = 12.4 Hz, $^3J_{H,H}$ = 3.8 Hz, 1H, 7H), 2.07−2.02 (m, 1H, 11H), 1.92−1.73 (m, 4H, 3H/8H/9H/10H), 1.65 (s, 3H, 12H), 1.58−1.35 (m, 5H, 3H/8H/9H/10H/11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4 (C13), 133.9 (C4), 129.5 (C14), 127.1 (C15), 125.8 (C16), 121.6 (C5), 76.4 (C6), 59.8 (C2), 54.7 (C7), 39.7 (C11), 30.3 (C3), 30.2 (C8), 26.6 (C9), 23.8 (C12), 23.6 (C10). IR (solid): ν = 2928, 2901, 2857, 1727, 1681, 1606, 1446, 1093, 754, 699, 551 cm^{-1}.

1-Methyl-14-oxatetracyclo[11.3.1.$0^{2,7}$.$0^{8,13}$]heptadeca-2,4,6-triene ((1*R**, 8*R**, 13*S**)-**32**): R_f: 0.18 (pentane/CH_2Cl_2, 6:4; phosphomolybdic acid). Mp: 69.5−71.9 °C. HRMS (ESI): calculated for $C_{17}H_{22}O$ + Na^+ = 265.1568, found = 265.1576; for $2C_{17}H_{22}O$ + Na^+ = 507.3239, found = 507.3238. Elemental anal. calculated for $C_{17}H_{22}O$: C, 84.25%; H, 9.15%; O, 6.60%; found: C, 84.03%; H, 9.23%; O, 6.84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31−7.27 (m, 2H, 3H/6H), 7.20−7.16 (m, 2H, 4H/5H), 3.62 (dd, $^3J_{H,H}$ = 11.9 Hz, $^3J_{H,H}$ = 5.1 Hz, 1H, 15H), 3.32 (dt, $^3J_{H,H}$ = 12.2 Hz, $^3J_{H,H}$ = 2.8 Hz, 1H, 15H), 2.69 (dd, $^3J_{H,H}$ = 12.2 Hz, $^3J_{H,H}$ = 2.8 Hz, 1H, 8H), 2.27−2.21 (m, 1H, 9H), 2.02−1.95 (m, 1H, 10H), 1.89 (tt, $^3J_{H,H}$ = 13.4 Hz, $^3J_{H,H}$ = 4.4 Hz, 1H, 11H), 1.81 (dd, $^2J_{H,H}$ = 12.6 Hz, $^4J_{H,H}$ = 2.5 Hz, 1H, 17H), 1.76−1.64 (m, 3H, 9H/12H/16H), 1.56−1.45 (m, 3H, 10H/11H/17H), 1.43 (s, 3H, 18H), 1.36 (dt, $^2J_{H,H}$ = 13.4 Hz, $^3J_{H,H}$ = 4.4 Hz, 1H, 12H), 1.22−1.17 (m, 1H, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5 (C2), 140.4 (C7), 126.3/126.2 (C4/C5), 124.7/124.4 (C3/C6), 70.8 (C13), 60.2 (C15), 46.5 (C17), 46.4 (C8), 40.8 (C16), 39.9 (C12), 33.8 (C1), 28.3 (C18), 27.3 (C10), 25.0 (C9), 20.9 (C11). IR (ATR): ν = 2941, 2926, 2905, 2864, 2849, 1484, 1443, 1263, 1097, 1061, 763, 527 cm^{-1}.

Spiroether ***37a*** *and Oxabicyclononane* ***39a***. In a flame-dried round-bottomed flask, phenylacetone **35a** (600 mg, 4.5 mmol) and TMS-ether **6a** (1.0 mL, 4.5 mmol) were dissolved in absolute CH_2Cl_2 (30 mL) at −20 °C, rt, or reflux and stirred for 5 min under N_2. TMSOTf (160 μL, 1 mmol) was added, and the resulting mixture was stirred at −20 °C, rt, or reflux for 4 h. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow oil was analyzed by ^{1}H NMR spectroscopy to identify the ratio of isomers. Purification of the reaction mixture stirred at rt by column chromatography (pentane/Et_2O = 95:5 to 9:1) gave a mixture of **39a** (110 mg, 0.5 mmol, 12%) and analytical probe **37a** as colorless oils.

1,9-Dimethyl-10-oxatricyclo[7.3.1.$0^{2,7}$]-trideca-2,4,6-triene (**39a**): R_f: 0.30 (pentane/Et_2O, 9:1; phosphomolybdic acid). HRMS (ESI): calculated for $C_{14}H_{18}O$ + Na^+ = 225.1250, found = 225.1242. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33−7.29 (m, 1H, 3H), 7.20−7.08 (m, 3H, 4H/5H/6H), 3.68 (dd, $^3J_{H,H}$ = 12.0 Hz, $^3J_{H,H}$ = 5.2 Hz 1H, 11H), 3.43 (dt, $^3J_{H,H}$ = 12.0 Hz, $^2J_{H,H}$ = 2.7 Hz, 1H, 11H), 2.99 (s, 2H, 8H), 1.76−1.68 (m, 2H, 12H/13H), 1.59 (d, $^2J_{H,H}$ = 12.0 Hz, 1H, 13H), 1.43 (s, 3H, 14H), 1.31 (s, 3H, 15H), 1.25 (d, $^3J_{H,H}$ = 12.0 H, 1H, 12H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7 (C2), 137.3 (C7), 127.5/126.2/126.1 (C4/C5/C6), 124.7 (C3), 70.4 (C9), 61.1 (C11), 45.7 (C13), 41.5 (C8), 40.4 (C12), 33.7 (C1), 30.1 (C15), 28.2 (C14). IR (thin film): ν = 2957, 2927, 2868, 1489, 1456, 1374, 1258, 1184, 1091, 759, 721 cm^{-1}.

2-Benzyl-2,4-dimethyl-3,6-dihydro-2*H*-pyran (**37a**): R_f: 0.48 (pentane/Et_2O, 9:1; phosphomolybdic acid). HRMS (ESI): calculated for $C_{14}H_{18}O$ + Na^+ = 225.1250, found = 225.1242. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30−7.26 (m, 2H, 12H), 7.24−7.20 (m, 3H, 11H/13H), 5.43 (s, 1H, 5H), 4.25−4.11 (m, 2H, 6H), 2.82 (s, 2H, 9H), 2.06 (d, $^2J_{H,H}$ = 12.0 Hz, 1H, 3H), 1.72−1.66 (m, 4H, 3H/8H), 1.12 (s, 3H, 7H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (C10), 130.8 (C11), 130.6 (C4), 128.0 (C12), 126.3 (C13), 118.8 (C5), 72.7 (C2), 61.4 (C6), 46.4 (C9), 39.1 (C3), 23.5 (C8), 23.1 (C7).

Oxabicyclononane Derivatives ***39b*** *and* ***40b***. In a flame-dried round-bottomed flask, 3-methoxyphenylacetone **35b** (985 mg, 6 mmol) and TMS-ether **6a** (1.2 mL, 6 mmol) were dissolved in absolute CH_2Cl_2 (30 mL) at −20 °C, rt, or reflux and stirred for 5 min under N_2. TMSOTf (220 μL, 1.2 mmol) was added, and the resulting mixture was stirred at −20 °C, rt, or reflux for 4 h. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow oil was analyzed by NMR spectroscopy to identify the ratio of isomers. Purification of the reaction mixture stirred at reflux by column chromatography (pentane/Et_2O, 95:5 → 9:1) gave **40b** (718 mg, 3.1 mmol, 51%) as a colorless oil and **39b** (378 mg, 1.6 mmol, 27%) as colorless crystals.

5-Methoxy-1,9-dimethyl-10-oxatricyclo[7.3.1.$0^{2,7}$]-trideca-2,4,6-triene (**40b**): R_f: 0.29 (pentane/CH_2Cl_2/Et_2O, 1:1:0.1; phosphomolybdic acid). HRMS (ESI): calculated for $C_{15}H_{20}O_2$ + Na^+ = 255.1361, found = 255.1362. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, $^3J_{H,H}$ = 8.8 Hz, 1H, 3H), 6.74 (dd, $^3J_{H,H}$ = 8.8 Hz, $^4J_{H,H}$ = 2.5 Hz, 1H, 4H), 6.64 (d, $^4J_{H,H}$ = 2.5 Hz, 1H, 6H), 3.79 (s, 3H, 16H), 3.67 (dd, $^3J_{H,H}$ = 12.0 Hz, $^2J_{H,H}$ = 5.0 Hz, 1H, 11H), 3.43 (dt, $^3J_{H,H}$ = 12.0 Hz, $^2J_{H,H}$ = 2.7 Hz, 1H, 11H), 2.96 (s, 2H, 8H), 1.73−1.65 (m, 2H, 12H/13H), 1.56 (d, $^2J_{H,H}$ = 12.4 Hz, 1H, 13H), 1.40 (s, 3H, 14H), 1.29 (s, 3H, 15H), 1.23−1.18 (m, 1H, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8 (C5), 138.6 (C7), 135.0 (C2), 125.7 (C3), 112.2/112.1 (C4/C6), 70.5 (C9), 61.2 (C11), 55.3 (C16), 46.0 (C13), 41.8 (C8), 40.5 (C12), 33.2 (C1), 30.1 (C15), 28.3 (C14). IR (thin film): ν = 2954, 2929, 2873, 2841, 1578, 1465, 1247, 1077, 770, 742 cm^{-1}.

3-Methoxy-1,9-dimethyl-10-oxatricyclo[7.3.1.$0^{2,7}$]-trideca-2,4,6-triene (**39b**): R_f: 0.40 (pentane/CH_2Cl_2/Et_2O, 1:1:0.1; phosphomolybdic acid). Mp: 91.8−95.8 °C. HRMS (ESI): calculated for $C_{15}H_{20}O_2$ + Na^+ = 255.1356, found = 255.1353. Elemental anal. calculated for $C_{15}H_{20}O_2$: C, 77.55%; H, 8.68%; O, 13.77%; found: C, 77.32%; H, 8.80%; O, 13.98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.09 (t, $^3J_{H,H}$ = 7.9 Hz, 1H, 5H), 6.71 (d, 1H, $^3J_{H,H}$ = 7.9 Hz, 6H), 6.69 (d, $^3J_{H,H}$ = 7.9 Hz, 1H, 4H), 3.78 (s, 3H, 16H), 3.66 (dd, $^3J_{H,H}$ = 12.0 Hz, $^2J_{H,H}$ = 5.0 Hz, 1H, 11H), 3.38 (ddd, $^3J_{H,H}$ = 12.8 Hz, $^3J_{H,H}$ = 12.0 Hz, $^2J_{H,H}$ = 2.6 Hz, 1H, 11H), 3.00 (d, $^2J_{H,H}$ = 18.3, 1H, 8H), 2.87 (d, $^2J_{H,H}$ = 18.3, 1H, 8H), 1.75 (d, $^2J_{H,H}$ = 12.7 Hz, 1H, 13H), 1.64 (d, $^2J_{H,H}$ = 13.0 Hz, 1H, 12H), 1.59−1.56 (m, 1H, 12H), 1.55 (s, 3H, 14H), 1.47 (d, $^2J_{H,H}$ = 12.7 Hz, 1H, 13H), 1.27 (s, 3H, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 158.6 (C3), 139.9 (C7), 130.6 (C2), 126.7 (C5), 120.5 (C6), 109.0 (C4), 70.1 (C9), 61.9 (C11), 55.2 (C16), 48.3 (C13), 42.1 (C8), 37.0 (C12), 33.9 (C1), 30.1 (C15), 28.9 (C14). IR (solid): ν = 3008, 2964, 2925, 2873, 1579, 1467, 1246, 1068, 924, 770 cm^{-1}.

Oxabicyclononane Derivative ***39c***. In a flame-dried round-bottomed flask, 4-methoxyphenylacetone **35c** (1.642 mg, 10 mmol) and TMS-ether **6a** (2.0 mL, 10 mmol) were dissolved in absolute CH_2Cl_2 (30 mL) at −20 °C, rt, or reflux and stirred for 5 min under N_2. TMSOTf (360 μL, 2 mmol) was added, and the resulting mixture was stirred at −20 °C, rt, or reflux for 4 h. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow oil was analyzed by NMR spectroscopy to identify the ratio of isomers. Purification of the reaction mixture stirred at rt by column chromatography (pentane/Et_2O, 95:5 → 8:2) gave **39c** (711

mg, 3.1 mmol, 31%) as a colorless oil. Fifty-eight milligrams of the racemate was separated by chiral SFC (CHIRALPAK IA; CO_2/*i*PrOH, 96:4) to get 22 and 25 mg, respectively, of the two enantiomers [HPLC-ee: 86 and 89%, α_D = 27.1 and −27.9° (each ca. 1.00, MeOH)].

4-Methoxy-1,9-dimethyl-10-oxatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene (**39c**): R_f: 0.35 (pentane/Et_2O, 8:2; phosphomolybdic acid). HRMS (ESI): calculated for $C_{15}H_{20}O_2$ + H^+ = 233.1536, found = 233.1537. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.01 (d, $^3J_{H,H}$ = 8.5 Hz, 1H, 6H), 6.85 (d, $^4J_{H,H}$ = 2.4 Hz, 1H, 3H), 6.73 (dd, $^3J_{H,H}$ = 8.5 H, $^4J_{H,H}$ = 2.4 Hz, 1H, 5H), 3.80 (s, 3H, 16H), 3.66 (dd, $^3J_{H,H}$ = 12.0 Hz, $^2J_{H,H}$ = 5.1 Hz, 1H, 11H), 3.44 (dt, $^3J_{H,H}$ = 12.0 Hz, $^2J_{H,H}$ = 2.7 Hz, 1H, 11H), 2.91 (s, 2H, 8H), 1.72−1.66 (m, 2H, 12H/13H), 1.56 (d, $^2J_{H,H}$ = 12.6 Hz, 1H, 13H), 1.40 (s, 3H, 14H), 1.29 (s, 3H, 15H), 1.25 (d, $^3J_{H,H}$ = 12.6 H, 1H, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1 (C4), 144.0 (C2), 129.4 (C7), 128.3 (C6), 111.4 (C5), 110.5 (C3), 70.5 (C9), 61.1 (C11), 55.4 (C16), 45.6 (C13), 40.7 (C8), 40.3 (C12), 34.0 (C1), 30.1 (C15), 28.2 (C14). IR (thin film): ν = 2955, 2928, 2913, 2873, 2833, 1611, 1495, 1112, 1058, 907, 779 cm^{-1}.

Oxabicyclononane Derivative ***40d***. In a flame-dried round-bottomed flask, 3-chlorophenylacetone **35d** (200 mg, 1.1 mmol) and TMS-ether **6a** (220 μL, 1.1 mmol) were dissolved in absolute $CHCl_3$ (5 mL) and stirred for 5 min under N_2. TMSOTf (40 μL, 0.22 mmol) was added, and the resulting mixture was stirred at reflux for 4 h. After 2 h, an additional amount of TMSOTf (40 μL, 0.22 mmol) was added. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow oil was analyzed by NMR spectroscopy to identify the ratio of isomers. Purification of the reaction mixture by column chromatography (pentane/Et_2O, 97:3) gave **40d** (116 mg, 0.49 mmol, 41%) as a colorless oil.

5-Chloro-1,9-dimethyl-10-oxatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene **40d**: R_f: 0.25 (pentane/Et_2O, 9:1; phosphomolybdic acid). HRMS (APCI): calculated for $C_{14}H_{17}OCl$ + H^+ = 237.1041, found = 237.1031. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, $^3J_{H,H}$ = 8.4 Hz, 1H, 3H), 7.12 (dd, $^3J_{H,H}$ = 8.4 Hz, $^4J_{H,H}$ = 2.4 Hz, 1H, 4H), 7.08−7.07 (m, 1H, 6H), 3.67 (dd, $^2J_{H,H}$ = 12.3 Hz, $^3J_{H,H}$ = 5.0 Hz, 1H, 11H), 3.38 (dt, $^2J_{H,H}$ = 12.3 Hz, $^3J_{H,H}$ = 2.9 Hz, 1H, 11H), 2.93 (s, 2H, 8H), 1.71−1.66 (m, 2H, 12H/13H), 1.57 (d, $^2J_{H,H}$ = 12.8 Hz, 1H, 13H), 1.39 (s, 3H, 14H), 1.29 (s, 3H, 15H), 1.22−1.17 (m, 1H, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2 (C7), 139.2 (C2), 131.8 (C5), 127.2 (C6), 126.3 (C4), 126.2 (C3), 70.3 (C9), 61.0 (C11), 45.5 (C13), 41.4 (C8), 40.3 (C12), 33.6 (C1), 30.0 (C15), 28.1 (C14). IR (thin film): ν = 2959, 2927, 2868, 1595, 1486, 1375, 1259, 1104, 1085, 1058, 877, 818, 782, 567 cm^{-1}.

Oxabicyclononane Derivative ***39e***. In a flame-dried round-bottomed flask, 4-bromophenylacetone **35e** (500 mg, 2.34 mmol) and TMS-ether **6a** (460 μL, 2.34 mmol) were dissolved in absolute $CHCl_3$ (10 mL) and stirred for 5 min under N_2. TMSOTf (85 μL, 0.47 mmol) was added, and the resulting mixture was stirred at reflux for 4 h. After 2 h, an additional amount of TMSOTf (85 μL, 0.47 mmol) was added. The progress of the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow oil was analyzed by NMR spectroscopy to identify the ratio of isomers. Twofold purification by column chromatography (pentane/Et_2O, 95:5) gave **39e** (60 mg, 0.21 mmol, 9%) as a colorless oil and **41** (22.3 mg, 0,064 mmol, 3%) as a colorless oil.

4-Bromo-1,9-dimethyl-10-oxatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene (**39e**): R_f: 0.32 (pentane/Et_2O, 95:5; phosphomolybdic acid). HRMS (APCI): calculated for $C_{14}H_{17}OBr$ + H^+ = 281.0535/283.0516, found = 281.1523/283.0507. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, $^4J_{H,H}$ = 2.1 Hz, 1H, 3H), 7.26 (dd, $^3J_{H,H}$ = 8.1 Hz, $^4J_{H,H}$ = 2.1 Hz, 1H, 5H), 6.96 (d, $^3J_{H,H}$ = 8.1 Hz, 1H, 6H), 3.66 (dd, $^2J_{H,H}$ = 12.3 Hz, $^3J_{H,H}$ = 5.1 Hz, 1H, 11H), 3.37 (dt, $^2J_{H,H}$ = 12.3 Hz, $^3J_{H,H}$ = 2.8 Hz, 1H, 11H), 2.89 (s, 2H, 8H), 1.71−1.65 (m, 2H, 12H/13H), 1.56 (dd, $^2J_{H,H}$ = 12.8 Hz, $^4J_{H,H}$ = 1.2 Hz, 1H, 13H), 1.39 (s, 3H, 14H), 1.29 (s, 3H, 15H), 1.27−1.20 (m, 1H, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1 (C2), 136.2 (C7), 129.2/129.1 (C5/C6), 127.9 (C3), 119.9 (C4), 70.2 (C9), 60.9 (C11), 45.3 (C13), 41.0 (C8), 40.2 (C12), 34.0 (C1), 30.0 (C15), 28.0 (C14). IR (thin film): ν = 2956, 2927, 2868, 1697, 1646, 1482, 1093, 853, 799, 780 cm^{-1}.

1-Methyl-1-(4′-bromobenzyl)-5,5-dimethyl-oxabicyclo[3.8]-dec-3-en (**41**): R_f: 0.36 (pentane/Et_2O, 95:5; phosphomolybdic acid). HRMS (ESI): calculated for $C_{19}H_{25}OBr$ + H^+ = 351.1143, found = 351.1144. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, $^3J_{H,H}$ = 8.3 Hz, 2H, 14H), 7.08 (d, $^3J_{H,H}$ = 8.3 Hz, 2H, 13H), 4.05−3.92 (m, 2H, 2H), 2.77 (d, $^2J_{H,H}$ = 13.5 Hz, 1H, 11H), 2.72 (d, $^2J_{H,H}$ = 13.5 Hz, 1H, 11H), 2.10−1.88 (m, 1H, 9H), 1.86−1.54 (m, 5H, 4H, 7H, 9H), 1.38 (td, $^3J_{H,H}$ = 6.5 Hz, $^4J_{H,H}$ = 2.0 Hz, 2H, 5H), 1.08 (s, 3H, 16H), 0.91 (m, 6H, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2 (C12), 132.4 (C14), 131.1 (C13), 124.5 (C8), 123.7 (C3), 120.3 (C15), 72.9 (C10), 64.3 (C2), 45.9 (C11), 44.1 (C7), 39.2 (C9), 35.4 (C5), 29.5 (C6), 28.7, 28.1 (C17, C18), 23.1 (C16), 23.0 (C4). IR (film): ν = 2948, 2920, 1488, 1451, 1383, 1073, 1011, 835, 805 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all newly isolated compounds; chromatograms for enantioselective SFC separations of compounds **32**, **39b**, **40b**, and **39c**; and Ortep plots of *trans*-**30**, (1*R**,8*R**,13*S**), and **39b**. 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.

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