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TOWARD THE SYNTHESIS OF (–)-CODEINE BY CHIRAL AUXILIARY-MEDIATED NITRONE CYCLOADDITION

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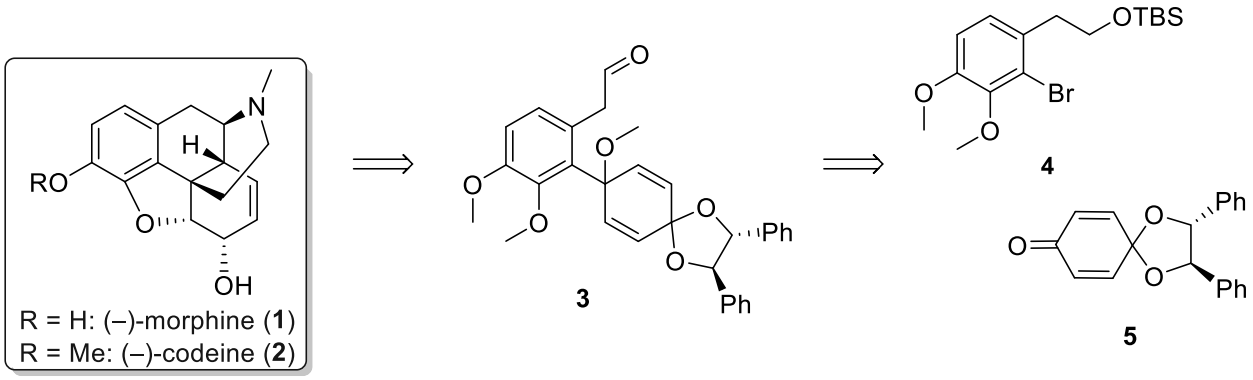
Abstract – Application of a C_2-symmetric dioxolane moiety as chiral auxiliary for an asymmetric intramolecular nitrone cycloaddition was studied as a possible key step for the enantioselective synthesis of (–)-codeine. A cycloaddition precursor bearing a 1,2-diphenylethylene acetal was selected that was readily accessible in ten steps from isovanillin. It underwent nitrone cycloaddition and after a consecutive transformation, an isoxazolidine intermediate with the absolute and relative configuration required for (–)-codeine was obtained.

INTRODUCTION

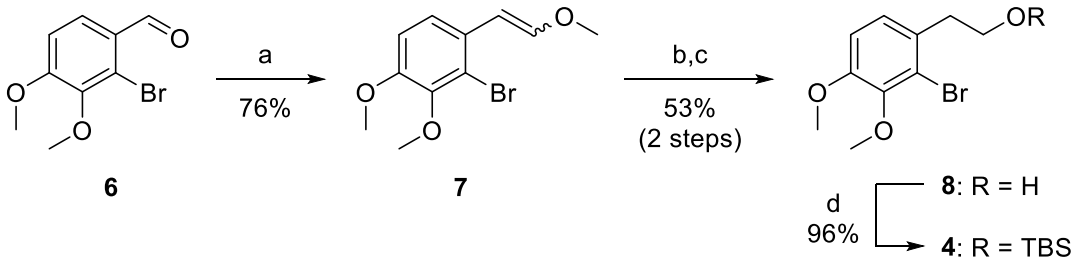
Morphine (**1**, Scheme 1) and codeine (**2**), isolated from opium poppy, exhibit a long history as analgesics and remain essential medicines for the treatment of severe pain despite numerous side effects.[1] Therefore, the design of flexible routes which enable the synthesis of alternative derivatives has been an important task until today. The high interest in morphine alkaloids is reflected by more than 30 total and formal syntheses published since 1952.[2] Among these, our group disclosed a total synthesis of (±)-codeine (**2**) in 2011, employing a highly diastereoselective intramolecular nitrone cycloaddition as a key step.[3] Herein, we report an approach to the enantioselective modification of our synthesis by utilization of a C_2-symmetric acetal moiety neighbouring the double bond in the nitrone cycloaddition precursor. Such chiral acetals have already been described and successfully used in cycloaddition reactions by the Figueredo group.[4] We envisioned that the easily accessible diphenylethylene acetal was well-suited for our studies. This selection led us to aldehyde **3** as the cycloaddition precursor. The spirocycle would, in analogy to our earlier work, be generated by addition of lithiated aryl bromide **4** to literature-known acetal **5**.[5]



Scheme 1. Retrosynthetic analysis

RESULTS AND DISCUSSION

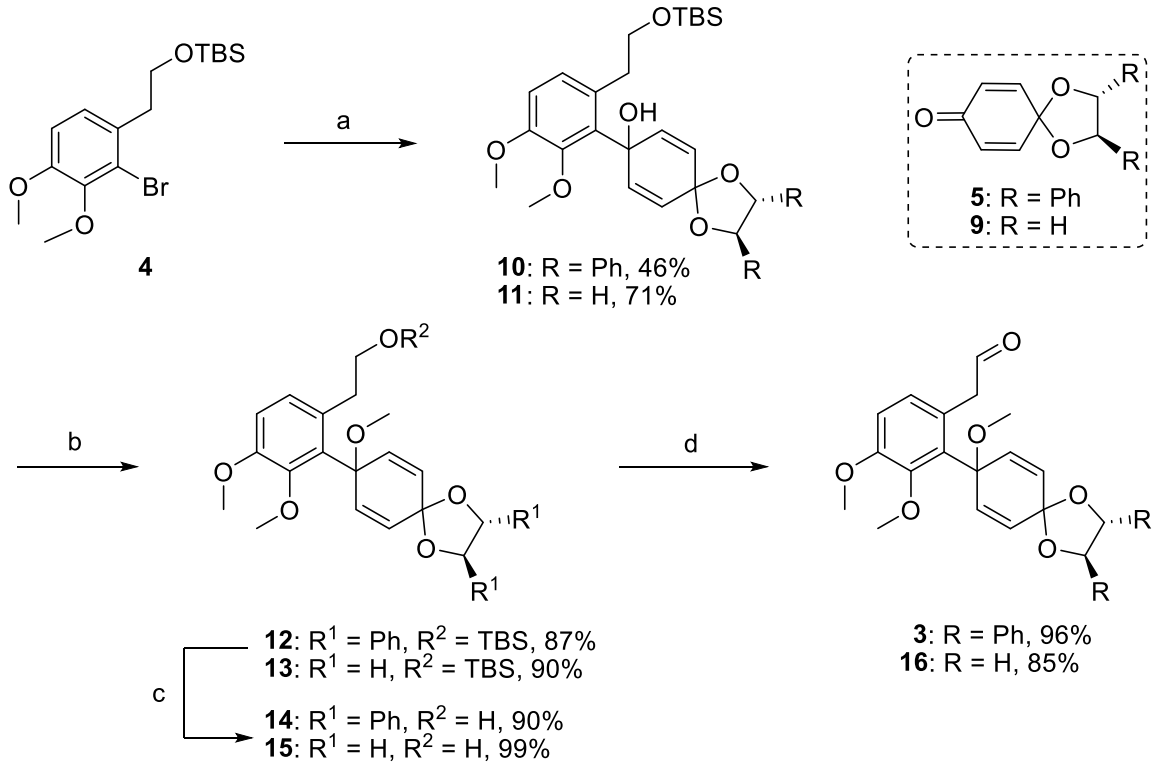
The aromatic fragment **4** was prepared from 2-bromoveratryl aldehyde (**6**)[6,7] as depicted in Scheme 2. After conversion of the isovanillin derivative **6** into enol ether **7**,[3] liberation of the carbonyl group by acid treatment and subsequent reduction furnished alcohol **8** which was protected as TBS ether to provide aryl bromide **4**.



Synthesis of aromatic fragment **4**. *Reagents and conditions:* a) Ph_3PCH_2OMeCl, KO*t*Bu, THF, 0 °C to rt, 3 h; b) 2 N HCl, THF, 60 °C, 9 h; c) $NaBH_4$, THF/MeOH (5 : 1), rt, 2 h; d) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, rt, 18 h.

Scheme 2

Second building block and carrier of the chiral information was *p*-benzoquinone monoacetal **5**, which could be synthesized from *p*-benzoquinone and (+)-hydrobenzoin within two steps (Scheme 3).[5] In addition, the achiral ethylene acetal **9**[8,9] was prepared in order to determine appropriate conditions for the following steps. Union of the two fragments was achieved by bromine-lithium exchange in **4** and subsequent addition to ketones **5** and **9**, respectively. Methylation of the resulting tertiary alcohols **10** and **11** led to methyl ethers **12** and **13**. The TBS groups were cleaved with TBAF to furnish primary alcohols **14** and **15**, which were readily oxidized with Dess–Martin periodinane. By this sequence, the aldehydes **3** and **16** were available for the key nitrone cycloaddition in good overall yields of 13% (**3**) and 22% (**16**), respectively, over eight steps from **6**.



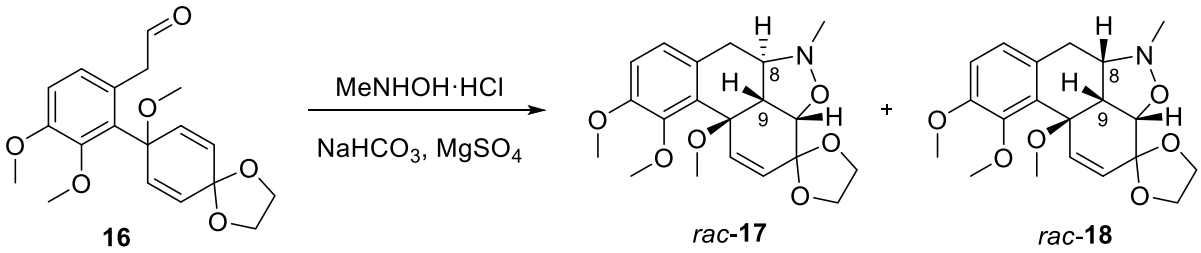
Synthesis of the cycloaddition precursors **3** and **16**. *Reagents and conditions:* a) *n*-BuLi, THF, –78 °C, 20 min, then acetal **5** or **9**, THF, to –65 °C, 4 h; b) MeI, NaH, THF, rt, 16 h; c) TBAF, THF, rt, 15 h; d) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 1.5 h.

Scheme 3

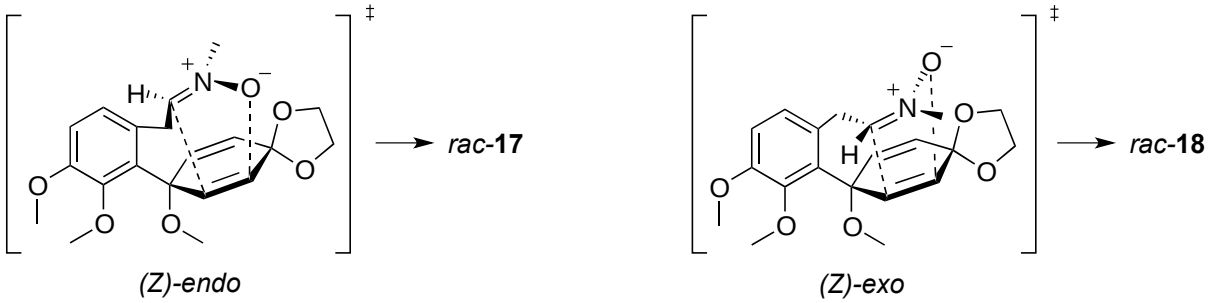
The nitrone cycloaddition was first investigated with the achiral precursor **16** (Table 1). Under the previously established conditions with MeCN as the solvent (Entry 1),[3] the yield of the desired 8,9-*trans* isoxazolidine **17** was only poor with concomitant formation of the 8,9-*cis* cycloadduct **18** and non-identifiable by-products. The epimers were easily separated and identified by the differing NOEs between H8 and H9. Thus, the presence of the dioxolane moiety led to a lower diastereoselectivity in comparison to the analogous dienone system used in our synthesis of racemic codeine,[3] where the 8,9-*trans* isoxazolidine was formed exclusively. Obviously, the energy difference between the favored (*Z*)-*endo* and the unfavored (*Z*)-*exo* transition state had decreased (Scheme 4).

We then undertook some variations of the reaction conditions in order to improve the efficiency of the cycloaddition. When changing the solvent to CH_2Cl_2 (Table 1, Entry 2), the yield improved drastically. However, it was observed that nitrone formation, which was very fast in MeCN, only proceeded slowly in CH_2Cl_2. Fortunately, dilution of the reaction mixture with CH_2Cl_2 after nitrone formation in MeCN further increased the yield of **17** to 60% along with an acceptable diastereomeric ratio (Entry 3).

Table 1. Intramolecular nitrone cycloaddition starting from achiral ethylene acetal **16**



Entry	Solvent (conc.)	Temp. & Time	**17** : **18**	Yield **17** (%)
1	MeCN (0.1 M)	0 °C, 1 h; then rt, 6 h	4.6 : 1	17
2	CH_2Cl_2 (0.1 M)	0 °C, 1 h; then rt, 6 h	3.5 : 1	39
3	1. MeCN (0.1 M) 2. CH_2Cl_2 (0.02 M)	1. 0 °C, 20 min 2. rt, 16 h	4.6 : 1	60

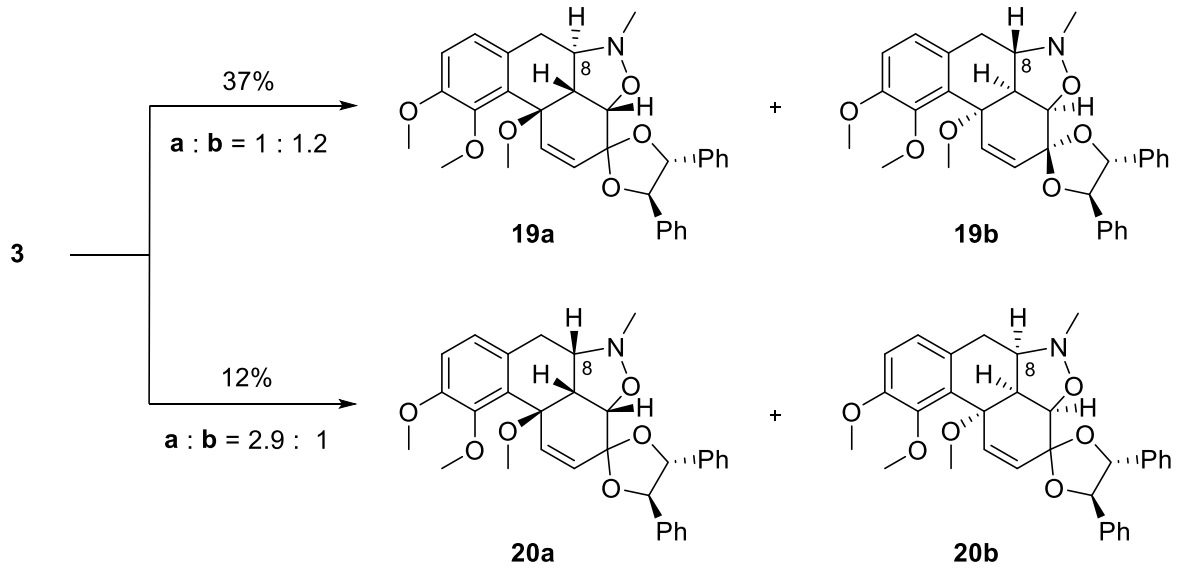


Proposed transition states of the nitrone cycloaddition leading to *rac*-**17** and the undesired 8,9-*cis* epimer *rac*-**18**

Scheme 4

With the optimized reaction conditions in hand, we undertook the nitrone cycloaddition with the chiral precursor **3**. As illustrated in Scheme 5, four diastereomeric products could be isolated: the inseparable isoxazolidines **19a** and **19b** as well as their C8-epimers, **20a** and **20b**. An asymmetric induction was observed; yet it was weak. The addition of titanum(IV) or zinc(II) Lewis acids led to lower or no product formation and reduced asymmetric induction.

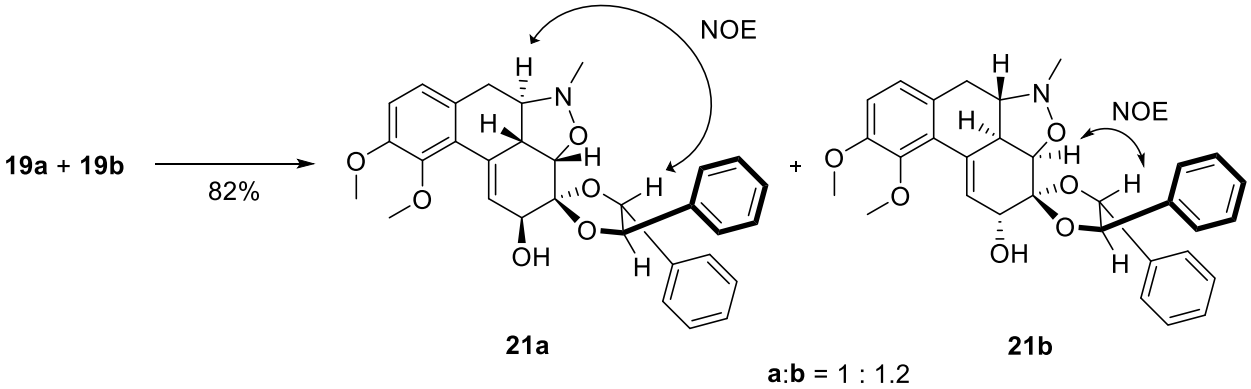
The configurations of the four structures were assessed by comparison of NOE measurements with calculated structures. This procedure provided hints that the minor component (**19a**) exhibits both the relative and absolute configuration corresponding to (–)-codeine.



Asymmetric intramolecular nitrone cycloaddition starting from diphenylethylene acetal **3**. *Reagents and conditions:* MeNHOH·HCl, $NaHCO_3$, $MgSO_4$, MeCN, 0 °C, 25 min, then CH_2Cl_2, 0 °C to rt, 16 h.

Scheme 5

As shown in Scheme 6, we found that acetals **19a** and **19b** underwent an allylic shift under acidic conditions furnishing alcohols **21a** and **21b** without attack on the acetal moiety. At this stage, separation of the two diastereomers was possible, and an enriched fraction of **21a** (*dr* = 9:1) was obtained after one chromatographical step. The observed NOEs depicted in Scheme 6 confirmed the proposed configurations. As this rearrangement was part of the synthetic pathway to (±)-codeine,[3] it can be included into our future work.



Acid-induced rearrangement to give allylic alcohols **21a** and **21b**; *Reagents and conditions:* 0.6 M HCl/MeCN, 75 °C, 4 h.

Scheme 6

In summary, a chiral intermediate for the enantioselective synthesis of (–)-codeine was provided with alcohol **21a**. This compound was accessible via asymmetric intramolecular nitrone cycloaddition of an olefin neighboring a C_2-symmetric diphenylethylene acetal. The cycloaddition precursor was readily available from isovanillin and (+)-hydrobenzoin. Further investigations should include optimization of the nitrone cycloaddition with variations of the acetal moiety or the *N*-substituent.

EXPERIMENTAL

THF, CH_2Cl_2 and toluene were dried and purified by passage through a MB-SPS-800 device using molecular sieves. The *p*-benzoquinone acetals **5**[5] and **9**,[8,9] 2-bromoveratrylaldehyde (**6**)[6,7] and $Ph_3PCH_2OCH_3Cl$[10] were prepared according to literature procedures. All other solvents and reagents were used as received. The solution of *n*-BuLi was titrated prior to use.[11] Reactions were performed under an argon atmosphere. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} 0.2 mm precoated plates. Flash column chromatography and dry column vauum chromatography[12] were carried out using silica gel (Merck, particle size 40–63 μm). Melting points were measured on a *Electrothermal Engineering* IA9100 instrument and are uncorrected. Infrared spectra were recorded on a *Thermonicolet* Avatar 360 instrument using ATR. NMR spectra were recorded on a *Bruker* DRX 500 P (^{1}H 500 MHz, ^{13}C 125 MHz) spectrometer or else on an Avance III 600 (^{1}H 600 MHz, ^{13}C 150 MHz) or an AC-300-P (^{1}H 300 MHz, ^{13}C 75 MHz). The multiplicities of ^{13}C NMR signals were determined using DEPT spectra. Mass spectra were recorded with an *Agilent* 5973N detector coupled with an *Agilent* 6890N GC (GC-MS, 70 eV) or a *Bruker* Esquire LC (direct injection as a methanolic NH_4OAc solution, ESI). HRMS spectra were recorded on a *Finnigan* MAT95 (EI, 70 eV) or a *Bruker Deltonik* Impact II (ESI-TOF). Elemental analysis was performed on a *Hekatech* EA 3000.

Wittig reaction[3] of 2-bromoveratryl aldehyde (6)[7]

To a suspension of Ph_3PCH_2OMeCl (1.08 g, 3.15 mmol) in THF (8 mL) at 0 °C was added KO*t*Bu (530 mg, 4.72 mmol), resulting in a deep red solution of the Wittig ylide. After stirring at 0 °C for 30 min, aldehyde **6** (643 mg, 2.62 mmol) was added in small portions (brightening of the solution). Stirring was continued for 45 min at 0 °C and 2 h at room temperature. Then, the reaction mixture was poured into a saturated aqueous NaCl solution (6 mL) and extracted with Et_2O (3x10 mL). The combined extracts were dried over $MgSO_4$ and the volatiles evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (pentane/Et_2O, 3:1) to give enol ether **7** (*E/Z*=1.4:1, 542 mg, 1.98 mmol, 76%) as a colorless oil.

Enol ether (*E/Z*)-**7**. R_f 0.39 (pentane/Et_2O, 3:1); IR 2935, 2836, 2056, 2030, 2009, 1734, 1717, 1698, 1639, 1590, 1548, 1516, 1484, 1458, 1393, 1337, 1276, 1253, 1216, 1152, 1129, 1098, 1026, 935, 917, 811, 697, 625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71, 3.76 (s, 3 H), 3.83, 3.84 (s, 3 H), 3.86, 3.86 (s, 3 H), 5.56

(d, *J* = 7.2 Hz, 1 H [*Z*-**7**]), 6.04 (d, *J* = 12.8 Hz, 1 H [*E*-**7**]), 6.18 (d, *J* = 7.2 Hz, 1 H [*Z*-**7**]), 6.81, 6.84 (d, *J* = 8.7 Hz, 1 H), 6.85 (d, *J* = 12.8 Hz, 1 H [*E*-**7**]), 7.05, 7.77 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 56.11 (CH_3), 56.19 (CH_3), 56.46 (CH_3), 60.32 (CH_3), 60.37 (CH_3), 60.66 (CH_3), 103.73 (CH), 104.35 (CH), 111.09 (CH), 111.66 (CH), 118.76 (C), 118.97 (C), 120.76 (CH), 125.39 (CH), 128.60 (C), 129.97 (C), 146.28 (C), 146.64 (C), 147.96 (CH), 149.30 (CH), 151.47 (C), 151.65 (C); GC-MS fraction 1: *m/z* 274 (99) $[^{81}M]^+$, 272 (100) $[^{79}M]^+$, 259 (37), 257 (36), 231 (14), 229 (15), 178 (96), 163 (42), 150 (25), 135 (51), 118 (15), 107 (22), 77 (25), 63 (19); fraction 2: *m/z* 274 (100) $[M]^+$, 272 (98), 259 (25), 257 (25), 231 (14), 229 (12), 178 (78), 163 (32), 150 (19), 135 (25), 118 (10), 107 (18), 77 (17), 63 (12). Anal. Calcd for $C_{11}H_{13}BrO_3$: C, 48.37; H, 4.80. Found: C, 48.48; H, 4.79.

Enol ether cleavage and reduction to give primary alcohol 8

Enol ether (*E/Z*)-**7** (539 mg, 1.97 mmol) was dissolved in THF (16 mL) and aqueous hydrochloric acid (2 M, 4.0 mL, 8.0 mmol) was added. The mixture was stirred at 60 °C for 9 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ solution (8 mL) was added under ice cooling. When gas evolution had ceased, the mixture was extracted with Et_2O (3x15 mL), and the combined organic extracts were washed with water, saturated aqueous NaCl solution and dried over $MgSO_4$. After removal of the volatiles under reduced pressure, the obtained crude aldehyde was dissolved in a mixture of THF (8 mL) and MeOH (2 mL). The solution was cooled to 0 °C, and $NaBH_4$ (82 mg, 2.17 mmol) was added in small portions. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 2 h. Then, saturated aqueous NH_4Cl solution was added, and the mixture was extracted with Et_2O (3x10 mL). The combined organic extracts were dried over $MgSO_4$ and the volatiles removed under reduced pressure. After purification by flash chromatography on silica gel (isohexane/EtOAc, 3:2 to 1:1), the alcohol **8** (270 mg, 1.04 mmol, 53% over two steps) was obtained as a colorless oil.

Alcohol **8**. R_f 0.35 (isohexane/EtOAc 1:1); IR 3348, 2998, 2937, 2879, 2833, 1594, 1484, 1458, 1402, 1265, 1207, 1146, 1029, 933, 856, 805, 753, 641, 546 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (br. s, 1 H), 3.00 (t, 2 H, *J* = 6.7 Hz), 3.86 (s, 3 H), 3.86 (t, *J* = 6.7 Hz, 2 H), 3.87 (s, 3 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 38.91 (CH_2), 56.10 (CH_3), 60.38 (CH_3), 62.16 (CH_2), 111.21 (CH), 120.35 (C), 125.84 (CH), 130.64 (C), 146.65 (C), 152.26 (C); GC-MS *m/z* 262 (25) $[^{81}M]^+$, 260 (26) $[^{79}M]^+$, 231 (100), 229 (100), 135 (11), 107 (14). Anal. Calcd for $C_{10}H_{13}BrO_3$: C, 46.00; H, 5.02. Found: C, 46.16; H, 5.13.

TBS protection of alcohol 8

To a solution of alcohol **8** (5.62 g, 21.5 mmol) in CH_2Cl_2 (200 mL) was added TBSCl (3.99 g, 26.5 mmol), imidazole (2.20 g, 32.3 mmol) and DMAP (131 mg, 1.08 mmol). After stirring at room temperature for 18 h, the supension was filtered and washed with water and saturated aqueous NaCl

solution. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography on silica gel (isohexane/EtOAc, 15:1) provided silyl ether **4** (7.73 g, 20.6 mmol, 96%) as a colorless oil.

Silyl ether **4**. R_f 0.33 (isohexane/EtOAc 15:1); IR 2998, 2952, 2929, 2856, 1995, 1508, 1485, 1473, 1401, 1361, 1293, 1255, 1207, 1146, 1093, 1060, 1034, 978, 937, 899, 831, 809, 774, 725, 663, 539 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.88 (s, 9 H), 2.94 (t, *J* = 7.0 Hz, 2 H), 3.80 (t, *J* = 7.0 Hz, 2 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 6.98 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ –5.39 (CH_3), 18.32 (C), 25.94 (CH_3), 39.21 (CH_2), 56.14 (CH_3), 60.38 (CH_3), 62.73 (CH_2), 111.10 (CH), 120.31 (C), 126.22 (CH), 131.34 (C), 146.44 (C), 152.03 (C); MS (ESI) *m/z* 375 $[^{79}M+H]^+$, 377 $[^{81}M+H]^+$; Anal. Calcd for $C_{16}H_{27}BrO_3Si$: C, 51.19; H, 7.25. Found: C, 51.11; H, 7.23.

Addition of lithiated 4 to *p*-benzoquinone acetals 5[5] and 9[8,9] (typical procedure)

A solution of bromide **4** (1.15 g, 3.06 mmol) in THF (15 mL) was cooled to –78 °C, and *n*-BuLi (1.1 M in hexanes, 2.7 mL, 2.95 mmol) was added dropwise over a period of 10 min. After further 20 min at –78 °C, diphenylethylene acetal **5** (749 mg, 2.46 mmol), dissolved in THF (7 mL), was added dropwise over a period of 15 min. Stirring was continued for 4 h while the temperature was raised to –65 °C. Then, the reaction mixture was diluted with EtOAc (7 mL) and allowed to warm to room temperature. Water (12 mL) was added, and the layers were seperated. The aqueous layer was extracted with EtOAc (3x15 mL), and the combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure, and flash chromatography on silica gel (pentane/EtOAc/Et_3N, 10:1:0.005) was carried out to furnish tertiary alcohol **10** (673 mg, 1.12 mmol, 46%) as a colorless oil.

Diphenylethylene acetal **10**. R_f 0.19 (pentane/EtOAc, 10:1); $[\alpha]^{20}_D$ –20.3 (*c* 1.0 in CH_2Cl_2); IR 3390, 3031, 2949, 2930, 2883, 2856, 1728, 1478, 1409, 1361, 1252, 1200, 1151, 1112, 1080, 1006, 981, 962, 913, 832, 812, 776, 759, 698, 650, 528 cm^{-1}; ^1H NMR ($CDCl_3$) δ –0.03 (s, 6 H), 0.83 (s, 9 H), 3.12–3.36 (m, 2 H), 3.70 (s, 3 H), 3.82 (s, 3 H), 3.84–3.90 (m, 2 H), 4.50 (br. s, 1 H), 4.81–4.91 (m, 2 H), 6.09 (d, *J* = 10.2 Hz, 2 H), 6.37 (d, *J* = 10.2 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 1 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 7.18–7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ –5.41 (CH_3), 18.40 (C), 25.96 (CH_3), 36.65 (CH_2), 55.81 (CH_3), 60.67 (CH_3), 65.78 (CH_2), 69.64 (C), 85.48 (CH), 99.81 (C), 111.70 (CH), 124.10 (CH), 124.64 (CH), 126.68 (CH), 126.79 (CH), 128.03 (CH), 128.21 (CH), 128.28 (CH), 128.37 (CH), 128.38 (CH), 130.98 (C), 135.38 (C), 136.55 (C), 136.86 (C), 137.21 (CH), 137.37 (CH), 147.41 (C), 151.58 (C); MS (ESI) *m/z* 601 $[M+H]^+$, 624 $[M+Na]^+$. HRMS *m/z* Calcd. for $C_{36}H_{44}O_6Si$ $[M]^+$: 600.2907. Found: 600.2888.

Ethylene acetal **11**. R_f 0.23 (pentane/EtOAc, 3:1); colorless oil; IR 3372, 3035, 2945, 2931, 2879, 2856, 1666, 1625, 1509, 1475, 1409, 1361, 1253, 1204, 1110, 1082, 1007, 958, 912, 888, 832, 812, 775, 727, 666 cm^{-1}; ^1H NMR ($CDCl_3$) δ –0.03 (s, 6 H), 0.83 (s, 9 H), 3.20 (t, *J* = 6.4 Hz, 2 H), 3.68 (s, 3 H), 3.82 (s,

3 H), 3.85 (t, *J* = 6.4 Hz, 2 H), 4.07 (s, 4 H), 4.61 (br. s, 1 H), 5.77 (d, *J* = 10.1 Hz, 2 H), 6.25 (d, *J* = 10.1 Hz, 2 H, 12-H), 6.82 (d, *J* = 8.5 Hz, 1 H), 6.92 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ –5.44 (CH_3), 18.39 (C), 25.94 (CH_3), 36.49 (CH_2), 55.81 (CH_3), 60.60 (CH_3), 64.90 (CH_2), 65.09 (CH_2), 65.72 (CH_2), 69.56 (C), 99.23 (C), 111.71 (CH), 123.64 (CH), 127.97 (CH), 130.88 (C), 135.45 (C), 137.07 (CH), 147.39 (C), 151.55 (C); MS (ESI) *m/z* 449 $[M+H]^+$; HRMS *m/z* Calcd. for $C_{24}H_{36}O_6Si$ $[M]^+$: 448.2281. Found: 448.2300.

Methylation of tertiary alcohols 10 and 11 (typical procedure)

Alcohol **10** (234 mg, 0.39 mmol) was dissolved in THF (3 mL), and NaH (60%, 78 mg, 1.95 mmol) was added in small portions. After stirring for 15 min at room temperature, methyl iodide (50 μL, 0.80 mmol) was added dropwise, and stirring was continued at room temperature for 16 h. Then, water (2 mL) was added with caution under ice cooling. The resulting mixture was extracted with Et_2O (3x5 mL), and the combined extracts were dried over $MgSO_4$. After evaporating the solvents in vacuo, dry column vacuum chromatography on silica gel (isohexane/EtOAc/Et_3N, 10:1:0.01) gave methyl ether **12** (208 mg, 0.34 mmol, 87%) as a white foam.

Diphenylethylene acetal **12**. R_f 0.23 (pentane/EtOAc, 3:1); $[\alpha]^{20}_D$ –15.9 (*c* 1.0 in CH_2Cl_2); IR 3061, 3031, 2952, 2931, 2855, 1677, 1475, 1408, 1361, 1292, 1253, 1199, 1115, 1091, 1054, 1023, 999, 957, 833, 810, 774, 753, 697, 651, 565 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.90 (s, 9 H), 3.12 (t, *J* = 7.2 Hz, 2 H), 3.23 (s, 3 H), 3.57 (s, 3 H), 3.81 (s, 3 H), 3.87 (t, *J* = 7.2 Hz, 2 H), 4.85 (d, *J* = 8.5 Hz, 1 H), 4.91 (d, *J* = 8.5 Hz, 1 H), 6.27 (s, 4 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 7.00 (d, *J* = 8.5 Hz, 1 H), 7.19–7.38 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ –5.25 (CH_3), 18.41 (C), 26.03 (CH_3), 38.32 (CH_2), 49.70 (CH_3), 55.82 (CH_3), 60.42 (CH_3), 65.94 (CH_2), 74.61 (C), 85.58 (CH), 85.65 (CH), 99.87 (C), 111.30 (CH), 126.54 (CH), 126.91 (CH), 127.25 (CH), 127.66 (CH), 128.24 (CH), 128.41 (CH), 128.43 (CH), 128.50 (CH), 131.52 (C), 133.58 (CH), 133.71 (CH), 135.11 (C), 136.49 (C), 136.83 (C), 147.43 (C), 151.67 (C); MS (ESI) *m/z* 615 $[M+H]^+$, 637 $[M+Na]^+$. Anal. Calcd for $C_{37}H_{46}O_6Si$: C, 72.28; H, 7.54. Found: C, 72.45; H, 7.64.

Ethylene acetal **13**. R_f 0.20 (pentane/EtOAc, 3:1); yellowish oil; IR 3038, 2949, 2932, 2879, 2857, 1509, 1474, 1408, 1374, 1361, 1338, 1292, 1251, 1201, 1091, 1056, 999, 957, 833, 810, 773, 730, 666, 622, 587 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 6 H), 0.89 (s, 9 H), 3.08 (t, *J* = 7.3 Hz, 2 H), 3.18 (s, 3 H), 3.54 (s, 3 H), 3.80 (s, 3 H), 3.85 (t, *J* = 7.3 Hz, 2 H), 4.09 (s, 4 H), 5.94 (d, *J* = 10.2 Hz, 2 H), 6.14 (d, *J* = 10.2 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 1 H), 6.98 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ –5.26 (CH_3), 18.39 (C), 26.01 (CH_3), 38.29 (CH_2), 49.44 (CH_3), 55.81 (CH_3), 60.24 (CH_3), 65.05 (CH_2), 65.17 (CH_2), 65.91 (CH_2), 74.50 (C), 99.23 (C), 111.27 (CH), 126.71 (CH), 128.49 (CH), 131.44 (C), 133.39 (CH), 135.10 (C), 147.35 (C), 151.63 (C); MS (ESI) *m/z* 463 $[M+H]^+$. Anal. Calcd for $C_{25}H_{38}O_6Si$: C, 64.90; H, 8.28. Found: C, 64.87; H, 8.34.

Desilylation with TBAF (typical procedure)

Silyl ether **12** (508 mg, 0.83 mmol) was dissolved in THF (8 mL), and TBAF (1 M in THF, 1.0 mL, 1.00 mmol) was added dropwise. The solution was stirred at room temperature for 15 h. Then, water (5 mL) and saturated aqueous NH_4Cl solution (2 mL) were added and the mixture was extracted with Et_2O (3x10 mL). The combined extracts were dried over $MgSO_4$ and the solvents removed under reduced pressure. The crude product was purified by dry column vacuum chromatography (isohexane/EtOAc, 10:1 to 1:2) to furnish the primary alcohol **14** (374 mg, 0.75 mmol, 90%) as a white foam.

Diphenylethylene acetal **14**. R_f 0.23 (pentane/EtOAc, 1:1); $[\alpha]^{20}_D$ –23.8 (*c* 1.0 in CH_2Cl_2); IR 3386, 3061, 3028, 2927, 1674, 1475, 1452, 1407, 1361, 1242, 1200, 1153, 1114, 1094, 1049, 997, 955, 867, 809, 752, 697, 650, 564, 528 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.91 (br. t, *J* = 4.9 Hz, 1 H), 3.12–3.19 (m, 2 H), 3.28 (s, 3 H), 3.60 (s, 3 H), 3.82 (s, 3 H), 3.87–3.96 (m, 2 H), 4.85 (d, *J* = 8.5 Hz, 1 H), 4.91 (d, *J* = 8.5 Hz, 1 H), 6.20 (d, *J* = 10.2 Hz, 2 H), 6.31 (d, *J* = 10.2 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 1 H), 7.02 (d, *J* = 8.5 Hz, 1 H), 7.17–7.44 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 36.87 (CH_2), 49.45 (CH_3), 55.82 (CH_3), 60.33 (CH_3), 64.80 (CH_2), 75.07 (C), 85.61 (CH), 85.67 (CH), 99.67 (C), 111.96 (CH), 126.52 (CH), 126.89 (CH), 127.76 (CH), 127.85 (CH), 128.09 (CH), 128.09 (CH), 128.30 (CH), 128.43 (CH), 128.49 (CH), 128.52 (CH), 131.25 (C), 133.09 (CH), 133.21 (CH), 135.04 (C), 136.33 (C), 136.65 (C), 147.44 (C), 151.82 (C); MS (ESI) *m/z* 501 $[M+H]^+$, 523 $[M+Na]^+$. HRMS *m/z* Calcd. for $C_{31}H_{32}O_6$ $[M]^+$: 500.2199. Found: 500.2170.

Ethylene acetal **15**. R_f 0.36 (pentane/EtOAc, 1:2); colorless oil; IR 3361, 3089, 2986, 2936, 2933, 1698, 1659, 1612, 1478, 1457, 1409, 1360, 1302, 1276, 1174, 1122, 1095, 1050, 1004, 963, 926, 911, 866, 814, 710, 673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.92 (br. t, *J* = 4.8 Hz, 1 H), 3.10 (t, *J* = 6.2 Hz, 2 H), 3.22 (s, 3 H), 3.56 (s, 3 H), 3.81 (s, 3 H), 3.88 (td, *J* = 4.8, 6.2 Hz, 2 H), 4.09 (s, 4 H), 5.97 (d, *J* = 10.4 Hz, 2 H), 6.07 (d, *J* = 10.4 Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 6.99 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 36.86 (CH_2), 49.19 (CH_3), 55.81 (CH_3), 60.17 (CH_3), 64.77 (CH_2), 65.09 (CH_2), 65.23 (CH_2), 74.98 (C), 99.07 (C), 111.94 (CH), 127.22 (CH), 127.83 (CH), 131.16 (C), 132.88 (CH), 135.04 (C), 147.39 (C), 151.79 (C); MS (ESI) *m/z* 349 $[M+H]^+$. HRMS *m/z* Calcd. for $C_{19}H_{24}NaO_6$ $[M+Na]^+$: 371.1465. Found: 371.1465.

Dess–Martin oxidation of primary alcohols 14 and 15 (typical procedure)

A stirred solution of alcohol **14** (345 mg, 0.69 mmol) in CH_2Cl_2 (7 mL) was treated with $NaHCO_3$ (174 mg, 2.07 mmol) and Dess–Martin periodinane (351 mg, 0.83 mmol). The reaction mixture was stirred at room temperature for 1.5 h. Then, Et_2O (5 mL) was added and after further stirring for 30 min, the suspension was filtered over a plug of celite. The solvents were removed *in vacuo* and the resulting crude product was purified by dry column vacuum chromatography (isohexane/EtOAc, 2:1) to afford aldehyde **3** (331 mg, 0.66 mmol, 96%) as a white foam.

Diphenylethylene acetal **3**. R_f 0.57 (pentane/EtOAc, 2:1); mp 75–78 °C; $[\alpha]^{20}_D$ –31.8 (*c* 1.0 in CH_2Cl_2); IR 3061, 3035, 2937, 2831, 2721, 1721, 1652, 1476, 1456, 1414, 1362, 1266, 1242, 1199, 1153, 1115, 1094, 1053, 996, 957, 868, 808, 753, 698, 649, 564, 528 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.12 (s, 3 H), 3.67 (s, 3 H), 3.75–3.78 (m, 2 H), 3.83 (s, 3 H), 4.84 (d, *J* = 8.5 Hz, 1 H), 4.92 (d, *J* = 8.5 Hz, 1 H), 6.01 (d, *J* = 10.2 Hz, 1 H), 6.02 (d, *J* = 10.2 Hz, 1 H), 6.32 (d, *J* = 10.2 Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 7.12–7.61 (m, 10 H), 9.62 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 48.71 (CH_3), 50.67 (CH_2), 55.72 (CH_3), 60.46 (CH_3), 74.94 (C), 85.61 (CH), 85.62 (CH), 99.64 (Cq, 14-C), 111.46 (CH, 6-C), 125.19 (C), 126.55 (CH), 126.89 (CH), 128.27 (CH), 128.40 (CH), 128.45 (CH), 128.48 (CH), 128.51 (CH), 128.79 (CH), 129.23 (CH), 132.63 (CH), 132.83 (CH), 135.22 (C), 136.32 (C), 136.65 (C), 147.84 (C), 152.84 (C), 200.49 (CH); MS (ESI) *m/z* 499 $[M+H]^+$, 521 $[M+Na]^+$. HRMS *m/z* Calcd. for $C_{31}H_{30}O_6$ $[M]^+$: 498.2042. Found: 598.2058.

Ethylene acetal **16**. R_f 0.44 (Et_2O); yellowish solid; mp 64 °C; IR 3035, 2939, 2883, 2826, 2707, 1711, 1652, 1509, 1477, 1458, 1414, 1304, 1265, 1242, 1209, 1113, 1092, 1046, 1010, 995, 952, 811, 765, 685, 664, 645, 623, 585, 567 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.06 (s, 3 H), 3.63 (s, 3 H), 3.72 (d, *J* = 1.5 Hz, 2 H), 3.81 (s, 3 H), 4.07–4.11 (m, 4 H), 5.89 (d, *J* = 10.2 Hz, 2 H), 5.99 (d, *J* = 10.2 Hz, 2 H), 6.82 (d, *J* = 8.3 Hz, 1 H), 6.88 (d, *J* = 8.3 Hz, 1 H), 9.58 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 48.44 (CH_3), 50.65 (CH_2), 55.73 (CH_3), 60.34 (CH_3), 65.07 (CH_2), 65.24 (CH_2), 74.85 (C), 99.05 (C), 111.47 (CH), 125.13 (C), 127.93 (CH), 129.19 (CH), 132.47 (CH), 135.22 (C), 147.82 (C), 152.83 (C), 200.47 (CH); MS (ESI) *m/z* 347 $[M+H]^+$. Anal. Calcd for $C_{19}H_{22}O_6$: C, 51.19; H, 7.25. Found: C, 51.11; H, 7.23.

Nitrone cycloaddition (typical procedure)

In MeCN (1 mL), a suspension of MeNHOH·HCl (18 mg, 0.21 mmol), $NaHCO_3$ (49 mg, 0.58 mmol) and $MgSO_4$ (75 mg, 0.62 mmol) was stirred for 10 min at room temperature and was then cooled to 0 °C. The aldehyde **3** (97 mg, 0.20 mmol) was added and after complete conversion of **3** (ca. 25 min), the reaction mixture was diluted with CH_2Cl_2 (10 mL), warmed to room temperature and stirred for 16 h. Then, the solids were removed by filtration and the solvents were removed under reduced pressure. Purification by flash chromatography on silica gel (isohexane/EtOAc, 2:1) furnished a mixture of the desired *trans* isoxazolidines **19a** and **19b** (**a**/**b** = 1:1.2, 42 mg, 72 μmol, 37%) as well as a mixture of the *cis* isoxazolidines **20a** and **20b** (**a**/**b** = 2.9:1, 17 mg, 23 μmol, 12%), both as brown oils.

Nitrone cycloaddition starting from diphenylethylene acetal 3

Trans isoxazolidines **19a** and **19b**: R_f 0.09 (pentane/EtOAc, 2:1); IR 3088, 3031, 2934, 2850, 1753, 1483, 1457, 1410, 1392, 1308, 1272, 1237, 1179, 1142, 1058, 973, 912, 806, 789, 765, 729, 698, 648, 606, 586, 528 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.74–2.80 (m, 1 H [**a**], 2 H [**b**]), 2.82–2.90 (m, 1 H [**a**], 1 H [**b**]), 2.85 (s, 3 H [**a**], 3 H [**b**]), 2.92–2.99 (m, 1 H [**a**], 1 H [**b**]), 3.09 (ddd as td, *J* = 4.7, 11.9 Hz, 1 H [**a**]), 3.33 (s, 3 H

[**a**/**b**]), 3.34 (s, 3 H [**a**/**b**]), 3.86 (s, 3 H [**b**]), 3.87 (s, 3 H [**a**]), 3.90 (s, 3 H [**b**]), 3.90 (s, 3 H [**a**]), 4.70 (d, *J* = 8.7 Hz, 1 H [**a**]), 4.79 (d, *J* = 8.7 Hz, 1 H [**b**]), 4.87 (d, *J* = 6.8 Hz 1 H [**a**], 1 H [**b**]), 5.09 (d, *J* = 8.7 Hz, 1 H [**b**]), 5.14 (d, *J* = 8.7 Hz, 1 H [**a**]), 6.01 (d, *J* = 10.5 Hz, 1 H [**a**]), 6.12 (d, *J* = 10.5 Hz, 1 H [**b**]), 6.76 (dd, *J* = 1.3, 10.5 Hz, 1 H [**b**]), 6.82–6.90 (m, 2 H [**a**], 2 H [**b**]), 6.85 (dd, *J* = 1.3, 10.5 Hz, 1 H [**a**]), 7.15–7.19 (m, 2 H [**a**]), 7.20–7.23 (m, 2 H [**b**]), 7.27–7.36 (m, 8 H [**a**]; 6 H [**b**]), 7.49–7.52 (m, 2 H [**b**]); ^{13}C NMR ($CDCl_3$) δ 34.00 (CH_2 [**a**/**b**]), 34.14 (CH_2 [**a**/**b**]), 43.73 (CH_3 [**a**]), 44.38 (CH_3 [**b**]), 51.35 (CH_3 [**a**/**b**]), 51.47 (CH_3 [**a**/**b**]), 52.82 (CH [**a**+**b**]), 55.93 (CH_3 [**a**/**b**]), 55.97 (CH_3 [**a**/**b**]), 60.75 (CH_3 [**a**/**b**]), 60.79 (CH_3 [**a**/**b**]), 63.21 (CH [**a**]), 63.94 (CH [**b**]), 76.81 (C [**b**]), 77.12 (C [**a**]), 78.53 (CH [**b**]), 79.02 (CH [**a**]), 84.57 (CH [**b**]), 84.74 (CH [**a**]), 86.27 (CH [**a**]), 87.00 (CH [**b**]), 101.92 (C [**b**]), 102.25 (C [**a**]), 113.02 (CH [**a**/**b**]), 113.09 (CH [**a**/**b**]), 124.77 (CH [**a**/**b**]), 124.89 (CH [**a**/**b**]), 126.28 (CH [**b**]), 126.71 (CH [**a**]), 127.24 (CH [**a**]), 128.21–128.54 (3x CH [**a**], C [**a**], 2x CH [**b**], C [**b**]), 128.76 (CH [**b**]), 128.82 (CH [**b**]), 129.82 (CH, C [**a**]), 130.04 (CH, C [**b**]), 131.05 (CH [**a**+**b**]), 131.83 (C [**a**/**b**]), 131.91 (C [**a**/**b**]), 135.40 (C [**b**]), 135.87 (C [**a**/**b**]), 136.00 (2x C [**a**]), 136.51 (C [**b**]), 149.23 (C [**a**/**b**]), 149.42 (C [**a**/**b**]), 152.53 (C [**a**/**b**]), 152.59 (C [**a**/**b**]); MS (ESI) *m/z* 528.3 $[M+H]^+$. HRMS *m/z* Calcd. for $C_{32}H_{33}NO_6$ $[M]^+$: 527.2308. Found: 527.2298.

Cis isoxazolidines **20a** and **20b**: R_f 0.18 (pentane/EtOAc, 2:1); IR 3058, 3032, 2929, 2851, 2247, 1728, 1488, 1456, 1413, 1363, 1267, 1238, 1176, 1117, 1071, 1041, 1022, 911, 869, 820, 804, 757, 728, 698, 647 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3 H [**b**]), 2.82 (s, 3 H [**a**]), 2.91–3.00 (m, 2 H [**a**], 2 H [**b**]), 3.12 (s, 3 H [**b**]), 3.16 (s, 3 H [**a**]), 3.22–3.28 (m, 1 H [**b**]), 3.29–3.36 (m, 1 H [**a**]), 3.54 (dd, *J* = 7.5, 11.3 Hz, 1 H [**b**]), 3.55 (dd, *J* = 7.9, 11.3 Hz, 1 H [**a**]), 3.73 (s, 3 H [**b**]), 3.77 (s, 3 H [**b**]), 3.83 (s, 3 H [**a**]), 3.88 (s, 3 H [**a**]), 4.53 (d, *J* = 8.3 Hz, 1 H [**a**]), 4.59 (d, *J* = 8.8 Hz, 1 H [**b**]), 4.64 (d, *J* = 11.3 Hz, 1 H [**b**]), 4.74 (d, *J* = 11.3 Hz, 1 H [**a**]), 4.90 (d, *J* = 8.8 Hz, 1 H [**b**]), 5.04 (d, *J* = 8.3 Hz, 1 H [**a**]), 5.85 (d, *J* = 10.3 Hz, 1 H [**a**]), 6.05 (d, *J* = 10.3 Hz, 1 H [**b**]), 6.69–6.77 (m, 4 H [**a**], 2 H [**b**]), 6.90 (d, *J* = 10.3 Hz, 1 H [**b**]), 6.91 (d, *J* = 10.3 Hz, 1 H [**a**]), 7.06–7.11 (m, 2 H [**a**]), 7.11–7.19 (2 H [**a**], 2 H [**b**]), 7.21–7.24 (m, 2 H [**b**]), 7.26–7.35 (m, 5 H [**a**], 6 H [**b**]), 7.36–7.40 (m, 2 H [**a**]); ^{13}C NMR ($CDCl_3$) δ 31.07 (CH_2 [**a**+**b**]), 44.37 (CH_3 [**a**+**b**]), 48.91 (CH [**a**+**b**]), 50.52 (CH_3 [**b**]), 50.65 (CH_3 [**a**]), 55.69 (CH_3 [**b**]), 55.79 (CH_3 [**a**]), 59.92 (CH_3 [**a**]), 60.13 (CH_3 [**b**]), 64.15 (CH [**a**+**b**]), 76.03 (C [**b**]), 76.29 (C [**a**]), 79.33 (CH [**a**+**b**]), 85.41 (2x CH [**a**], CH [**b**]), 86.00 (CH [**b**]), 104.10 (C [**a**+**b**]), 112.34 (CH [**a**+**b**]), 123.51 (CH [**b**]), 123.81 (CH [**a**]), 125.95 (CH [**a**]), 126.53 (CH [**b**]), 126.90 (CH [**b**]), 127.04 (CH [**a**]), 127.45 (CH [**a**]), 127.74–127.85 (2x CH [**a**], CH [**b**]), 128.32–238.53 (3x CH [**a**], 4x CH [**b**]), 128.93 (C [**a**+**b**]), 130.33 (C [**a**+**b**]), 136.32 (C [**b**]), 136.47 (C [**a**]), 136.60 (C [**a**] + C [**b**]), 137.11 (C [**a**]), 138.90 (CH [**a**]), 139.23 (CH [**b**]), 148.10 (C [**a**+**b**]), 151.56 (C [**a**+**b**]); MS (ESI) *m/z* 528.3 $[M+H]^+$. HRMS *m/z* Calcd. for $C_{32}H_{33}NO_6$ $[M]^+$: 527.2308. Found: 527.2309.

Nitrone cycloaddition starting from ethylene acetal 16

Trans isoxazolidine **17**: R_f 0.28 (EtOAc); yellow solid; mp 112–114 °C; IR 3384, 3088, 3045, 2975, 2938, 2836, 1670, 1483, 1457, 1412, 1394, 1310, 1273, 1237, 1182, 1129, 1068, 1043, 1009, 969, 949, 873, 806, 791, 744, 675, 604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.74 (dd, *J* = 11.0, 14.2 Hz, 1 H), 2.82–2.92 (m, 3 H), 2.89 (s, 3 H), 3.25 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 3.94–3.99 (m, 1 H), 3.99–4.02 (m, 1 H), 4.08–4.12 (m, 1 H), 4.12–4.17 (m, 1 H), 4.53 (d, *J* = 6.6 Hz, 1 H), 5.70 (d, *J* = 10.5 Hz, 1 H), 6.73 (dd, *J* = 1.6, 10.5 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 6.87 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 34.09 (CH_2), 43.69 (CH_3), 51.22 (CH_3), 52.48 (CH), 55.91 (CH_3), 60.69 (CH_3), 63.53 (CH), 64.58 (CH_2), 66.07 (CH_2), 77.20 (C), 78.62 (CH), 101.48 (C), 113.01 (CH), 124.79 (CH), 128.29 (C), 129.21 (CH), 131.64 (C), 131.76 (CH), 149.25 (C), 152.47 (C); MS (ESI) *m/z* 376.2 $[M+H]^+$. HRMS *m/z* Calcd. for $C_{20}H_{25}NO_6$ $[M]^+$: 375.1682. Found: 375.1681.

Cis isoxazolidine **18**: R_f 0.43 (EtOAc); yellow solid; mp 137–139 °C; IR 2932, 2891, 2834, 1721, 1508, 1483, 1455, 1421, 1388, 1362, 1289, 1263, 1228, 1186, 1115, 1064, 1042, 1022, 1009, 981, 955, 911, 878, 837, 795, 756, 721, 702, 675, 650, 625, 577, 551 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73 (s, 3 H), 2.80–2.90 (m, 1 H), 2.97–3.04 (m, 1 H), 3.06 (s, 3 H), 3.14–3.21 (m, 1 H), 3.44 (dd, *J* = 7.9, 11.5 Hz, 1 H), 3.78 (s, 3 H), 3.80 (ddd as td, *J* = 4.9, 6.8 Hz, 1 H), 3.82 (s, 3 H), 3.86 (ddd as q, *J* = 6.8 Hz, 1 H), 3.98 (ddd as q, *J* = 6.8 Hz, 1 Hz), 4.06 (ddd as td, *J* = 4.9, 6.8 Hz, 1 H), 4.49 (d, *J* = 11.5 Hz, 1 H), 5.68 (d, *J* = 10.5 Hz, 1 H), 6.80 (d, *J* = 10.5 Hz, 1 H), 6.81 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.67 (CH_2), 44.20 (CH_3), 50.37 (CH_3), 50.67 (CH), 55.65 (CH_3), 59.83 (CH_3), 64.90 (CH), 64.96 (CH_2), 66.37 (CH_2), 75.72 (C), 78.87 (CH), 103.88 (C), 112.29 (CH), 123.91 (CH), 125.46 (CH), 128.55 (C), 129.96 (C), 138.61 (CH), 148.30 (C), 151.62 (C); MS (ESI) *m/z* 376.2 $[M+H]^+$. HRMS *m/z* Calcd. for $C_{20}H_{25}NO_6$ $[M]^+$: 375.1682. Found: 375.1692.

Allylic rearrangement of the mixture of 19a and 19b

To a solution of isoxazolidines **19a** and **19b** (1:1.2, 15 mg, 28 μmol) in MeCN (0.25 mL) and water (0.25 mL) was added diluted hydrochloric acid (2 M, 0.1 mL, 0.20 mmol). The solution was stirred at 75 °C for 4 h. Then, water (0.5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3x2 mL). The combined extracts were washed with aqueous NaOH solution (2 N, 3 mL) and saturated aqueous NaCl solution (3 mL) and dried over $MgSO_4$. After removal of the solvents under reduced pressure, flash chromatography on silica gel (pentane/EtOAc, 1:3) provided the allylic alcohols **21a** and **21b** as a white solid (**a**/**b** = 1:1.2, 12 mg, 28 μmol, 82%), among which a fraction enriched in **21a** (*dr* = 9:1, 2.9 mg, 5.7 μmol) as well as a fraction enriched in **21b** (*dr* = 2.5:1, 4.1 mg, 8.0 μmol) could be obtained.

Allylic alcohol **21a**: R_f 0.31 (EtOAc/pentane, 3:1); IR (mixture of diastereomers): 3450, 3031, 2924, 2850, 1478, 1450, 1431, 1374, 1310, 1281, 1254, 1174, 1153, 1082, 1049, 1016, 991, 907, 868, 830, 803, 764,

729, 698, 648, 628, 595, 556, 528 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54 (d, *J* = 1.9 Hz, 1 H), 2.85 (s, 3 H), 2.87 (dd, *J* = 10.9, 13.9 Hz, 1 H), 2.95–3.03 (m, 2 H), 3.29 (ddd, *J* = 1.8, 8.8, 11.3 Hz, 1 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 4.40 (dd, *J* = 1.9, 6.4 Hz, 1 H), 4.72 (d, *J* = 8.7 Hz, 1 H), 4.96 (d, *J* = 8.8 Hz, 1 H), 5.25 (d, *J* = 8.7 Hz, 1 H), 6.83 (d, *J* = 8.7 Hz, 1 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 7.10–7.13 (m, 2 H), 7.17 (dd, *J* = 1.8, 6.4 Hz, 1 H), 7.25–7.28 (m, 3 H), 7.35–7.37 (m, 3 H), 7.39–7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 33.79 (CH_2), 44.17 (CH_3), 52.36 (CH), 56.10 (CH_3), 59.91 (CH_3), 66.85 (CH), 70.03 (CH), 75.07 (CH), 84.81 (CH), 87.52 (CH), 107.49 (C), 112.48 (CH), 122.56 (CH), 125.30 (CH), 126.42 (CH), 127.48 (CH), 127.87 (C), 128.38 (CH), 128.42 (CH), 128.54 (CH), 128.70 (CH), 128.81 (C), 135.84 (C), 136.12 (C), 148.27 (C), 151.75 (C); MS (ESI; mixture of diastereomers) *m/z* 514.3 $[M+H]^+$. HRMS (mixture of diastereomers) *m/z* Calcd. for $C_{31}H_{31}NO_6$ $[M]^+$: 513.2151. Found: 513.2132.

Allylic alcohol **21b**: R_f 0.27 (EtOAc/pentane, 3:1); IR see **21a**; ^1H NMR ($CDCl_3$) δ 2.59 (br. s, 1 H), 2.82–2.93 (m, 2 H), 2.95–3.04 (m, 1 H), 2.97 (s, 3 H), 3.25–3.31 (m, 1 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 4.43 (d, *J* = 6.4 Hz, 1 H), 4.84 (d, *J* = 9.0 Hz, 1 H), 4.98 (d, *J* = 9.3 Hz, 1 H), 5.14 (d, *J* = 9.0 Hz, 1 H), 6.82 (d, *J* = 8.3 Hz, 1 H), 6.89 (d, *J* = 8.3 Hz, 1 H), 7.15 (dd, *J* = 1.9, 6.4 Hz, 1 H), 7.24–7.31 (m, 5 H), 7.32–7.38 (m, 3 H), 7.39–7.45 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 33.61 (CH_2), 43.51 (CH_3), 52.28 (CH), 56.09 (CH_3), 59.82 (CH_3), 66.62 (CH), 70.43 (CH), 74.44 (CH), 85.59 (CH), 86.77 (CH), 106.94 (C), 112.54 (CH), 122.90 (CH), 125.30 (CH), 126.80 (CH), 127.81 (CH), 128.03 (C), 128.22 (CH), 128.57 (CH), 128.62 (CH), 128.70 (CH), 128.82 (C), 135.45 (2x C), 136.36 (C), 148.45 (C), 151.75 (C); MS (ESI) see **21a**. HRMS see **21a**.

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This paper is dedicated with our best wishes to Professor Masakatsu Shibasaki on the occasion of his 70th birthday.

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