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Building Blocks for (C^{15}–C^{3})-Modified Epothilone D Analogs

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Abstract—A promising potentially biologically active structure have been designed by isosteric rearrangement of the C^{15}–C^{3} fragment of epothilone D, and building blocks necessary for its assembly have been synthesized.

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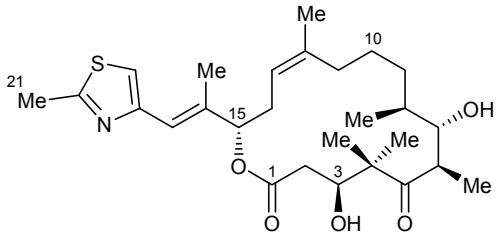
An important landmark in the chemotherapy of cancer was the discovery of taxol and implementation of tubulin-polymerizing antineoplastics (taxotere, paclitaxel) in medical practice [1, 2]. Later, a number of other natural compounds have been found to exhibit analogous effect (discodermolide, sarcodictyins, laulimalide, epothilones, etc.). Epothilones occupy a particular place in this series [3–5]. They are essentially more advantageous than taxol due to their very low sensitivity to P-glycoprotein efflux pump, activity against cancer cells overexpressing P-glycoprotein and other taxol-resistant cancer cell lines, and insensitivity toward some taxol-inactivating tubulin mutations [6–8]. Furthermore, the synthesis of epothilones is simpler than the synthesis of taxol. Among natural compounds with taxol-like mechanism of anticancer effect, epothilones are those for which total syntheses have been developed and structure–activity relationships have been studied in detail [9–15].

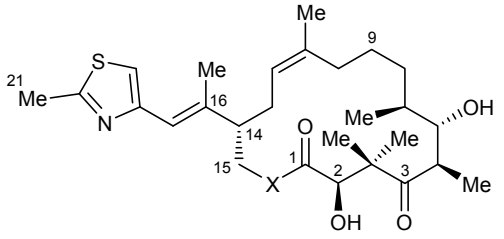
The main drawbacks of the use of epothilones in practice are their metabolic instability related to fast opening of the lactone ring *in vivo* with loss of activity and chemical instability due to opening of the epoxide ring by the action of nucleophiles, dehydration of the α-hydroxy carbonyl fragment, and possible transformations of the allylic alcohol fragment.

We previously planned to synthesize new metabolically and chemically more stable epothilone D (**I**) analogs, compounds **II** and **III** [16] with isosterically displaced methylene unit in the C^{15}–C^{3} fragment. We presumed that, unlike readily hydrolyzable *in vivo* macrolide **I**, its analogs **II** and **III** contain more stable lactam and lactone fragments, respectively (the C^{1}=O carbonyl group is sterically hindered and is stabilized by the C^{1}=O···HO–C^{2} hydrogen bond, and elimination of the C^{2}-hydroxy group is impossible). Such isosteric rearrangement of the C^{15}–C^{3} fragment of natural epothilone **I** has not been reported. This structural modification should affect the stability of the resulting compounds and change their conformation upon binding to tubulin, so that their biological activity should change. The above considerations determined the choice of compounds **II** and **III** as target structures. Compound **III** is an isostere of epothilone D (**I**), which is important from the viewpoint of estimation of the effect of modification of the C^{15}–C^{3} fragment on the biological activity of epothilones.

We have developed a retrosynthetic scheme which implies preparation of key building blocks **V**–**VII** starting from commercially available γ-butyrolactone



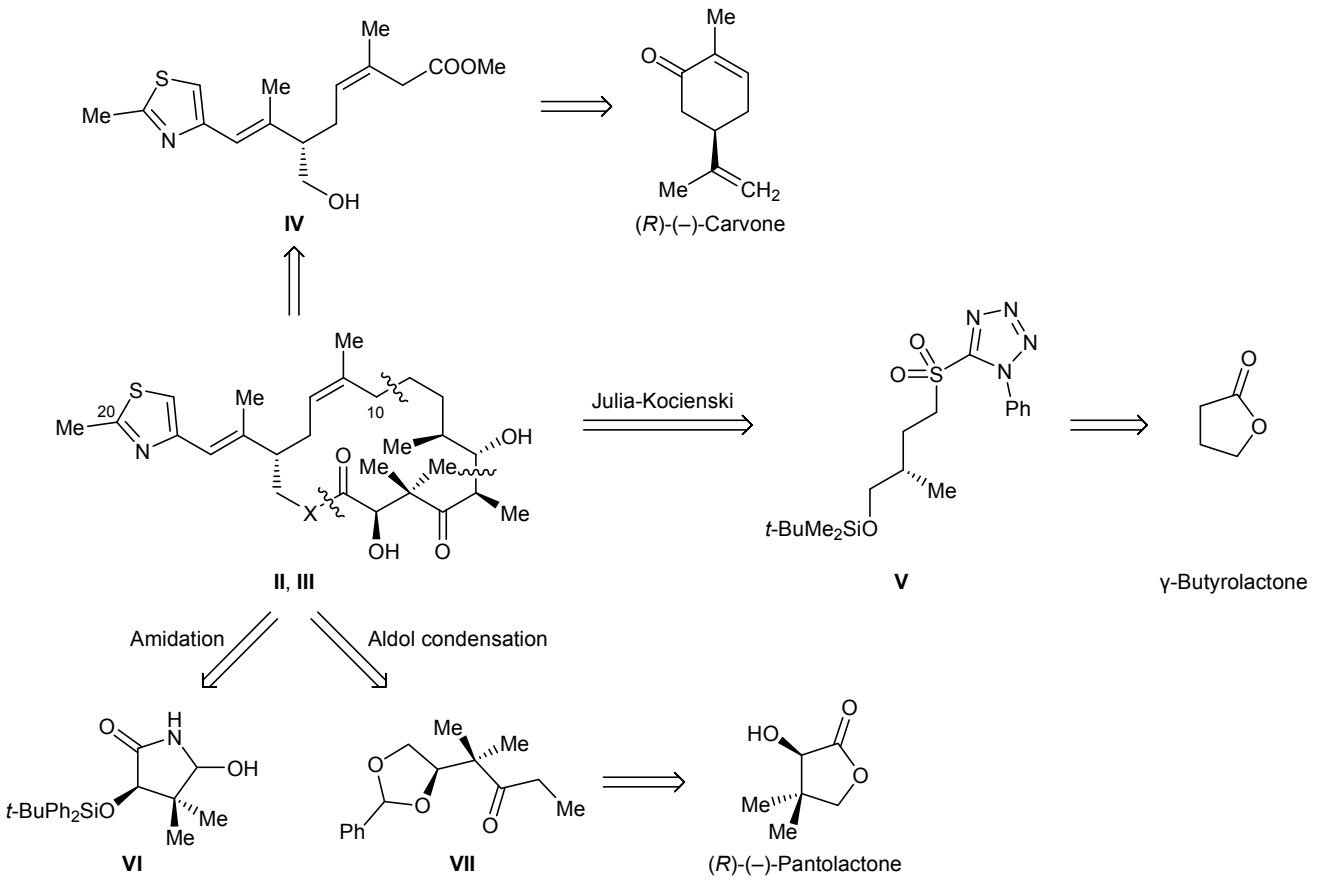
I



II, **III**

II, X = NH; **III**, X = O.

Scheme 1.

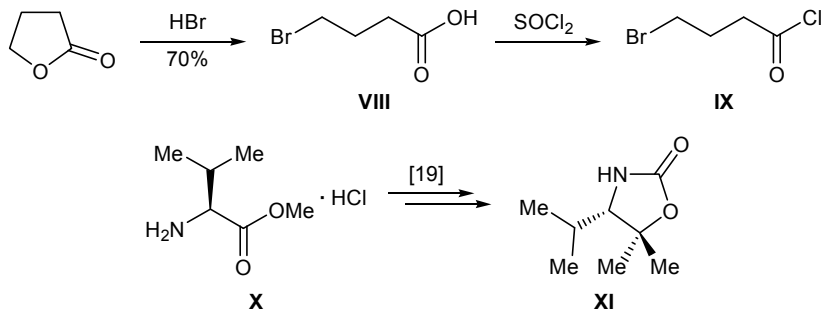


and (*R*)-(–)-pantolactone (Scheme 1). The synthesis of thiazolyl-substituted block **IV** from *R*-(–)-carvone was reported by us previously [17].

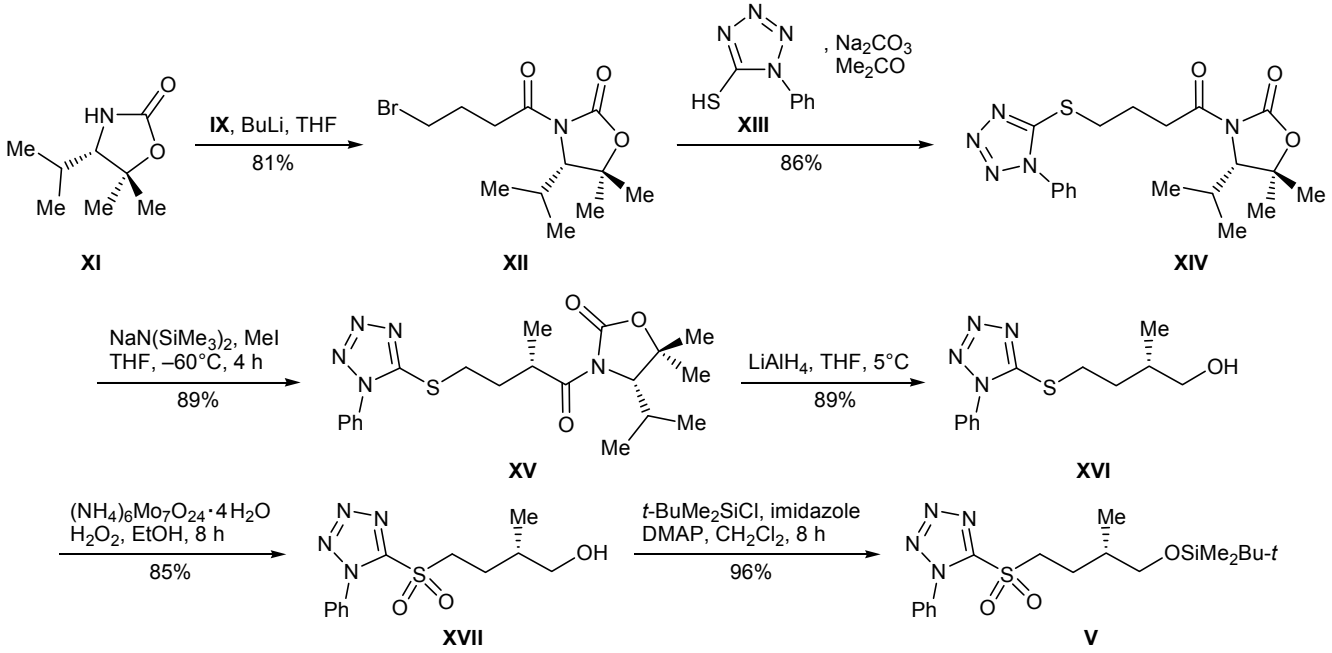
Sulfone **V** was synthesized from commercial γ-butyrolactone. The main problem was to introduce a methyl group into the 2-position of γ-butyrolactone with asymmetric induction. Insofar as direct alkylation methods did not ensure high enantioselectivity, we tried a roundabout way following the tested Evans oxazolidinone procedure [18]. Required acid chloride **IX** was prepared by standard methods from γ-butyrolactone through γ-bromobutyric acid (**VIII**), and substituted oxazolidinone **XI** was synthesized from L-valine methyl ester hydrochloride (**X**) according to [19] (Scheme 2).

Lithium derivative of **XI** was acylated with acid chloride **IX**, and *N*-(4-bromobutyryl)oxazolidinone **XII** thus obtained was brought into reaction with 1-phenyl-1*H*-tetrazole-5-thiol (**XIII**) [20]. The resulting compound **XIV** was treated with hexamethyldisilazane sodium salt to generate enolate which was alkylated with methyl iodide at –78°C. This alkylation step was characterized by high stereoselectivity, and the purity of **XV** attained 98% (according to the

Scheme 2.



Scheme 3.



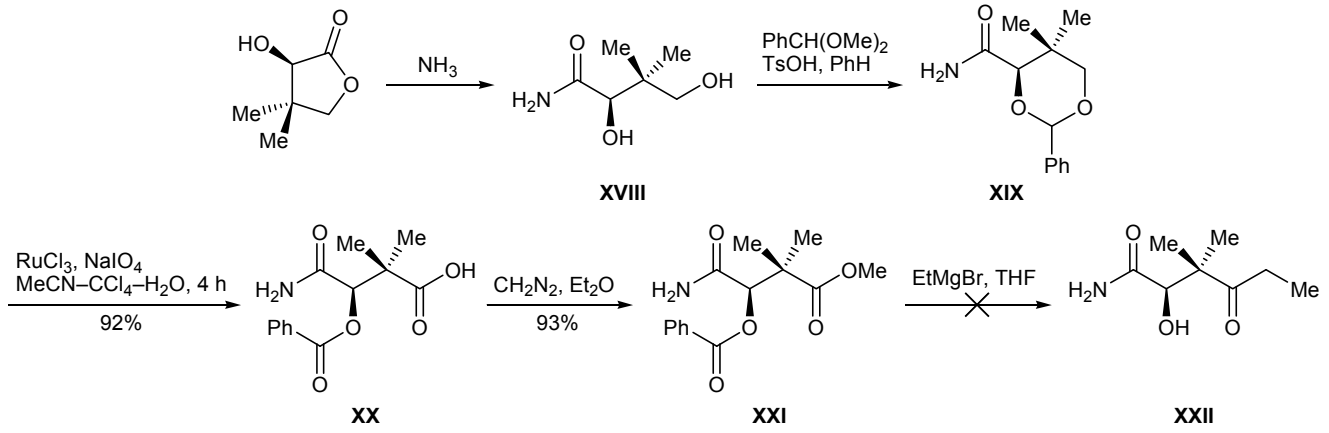
^{1}H NMR data). Removal of the chiral fragment from **XV** via reduction with $LiAlH_4$ gave sulfide **XVI** which was oxidized to sulfone **XVII**, and the hydroxy group in the latter was protected by silylation with *tert*-butylchloro(dimethyl)silane to obtain target building block **V** (Scheme 3).

Commercial (*R*)-(–)-pantolactone containing geminal methyl groups and properly oriented hydroxy group was an appropriate starting compounds for the synthesis of blocks **VI** and **VII**, which are necessary for assembling the polypropionate fragment of epothilone molecule.

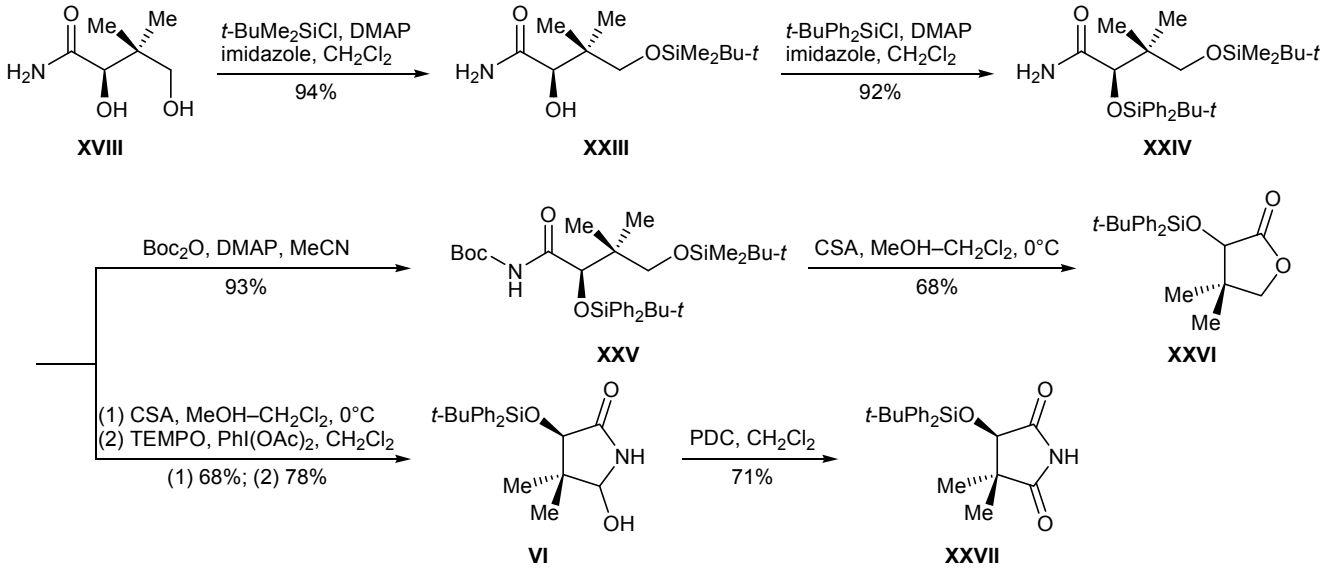
Chemodifferentiated ring opening of pantolactone to ω-hydroxy acid is inconvenient because of reversibility of the reaction. Therefore, we tried ring opening with amines taking into account that amide function can act as temporary protection of the carboxy group. By treatment of pantolactone with liquid ammonia we obtained amide **XVIII** which was converted in succession to acetal **XIX**, acid **XX**, and amido ester **XXI** (Scheme 4). However, the condensation of ester **XXI** with ethylmagnesium bromide gave no expected compound **XXII**.

In order to synthesize a more reactive substrate for the condensation with EtMgBr, compound **XVIII** was converted into orthogonally substituted amide **XXIV** (Scheme 5) which was protected at the NH_2 group by treatment with Boc_2O. Selective hydrolysis of *tert*-butyl(dimethyl)silyl ether **XXV** was expected to produce the corresponding primary alcohol which we

Scheme 4.

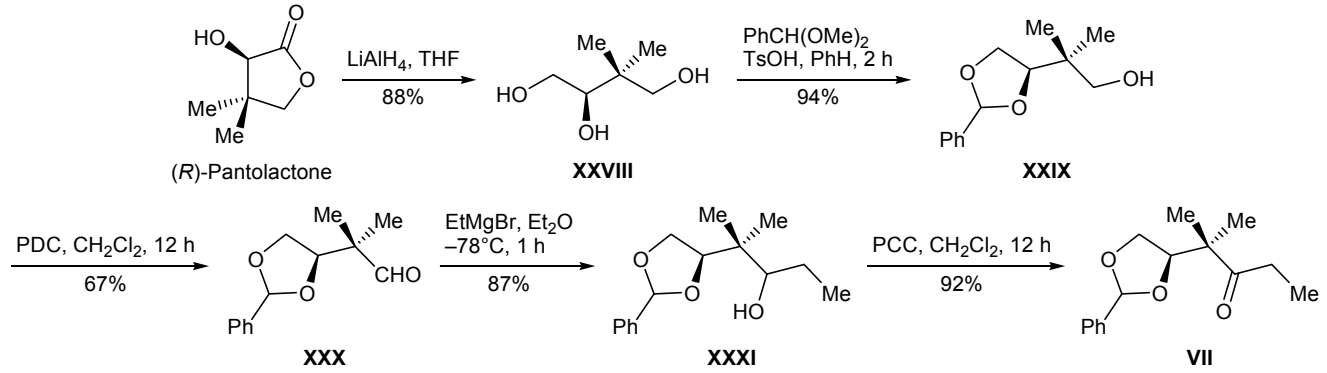


Scheme 5.



CSA stands for camphorsulfonic acid, and TEMPO, for 2,2,6,6-tetramethylpiperidine 1-oxyl.

Scheme 6.



planned to oxidize to aldehyde and react the latter with EtMgBr. However, the hydrolysis of **XXV** gave lactone **XXVI**. By selective hydrolysis of unprotected amido ester **XXIV** we obtained primary alcohol whose mild oxidation afforded cyclic aminal **VI**, and compound **VI** was oxidized with pyridinium dichromate (PDC) to lactam **XXVII**. Unfortunately, neither compound **XXVI** nor **XXVII** reacted with EtMgBr.

Following an alternative version of pantolactone decyclization, we synthesized known triol **XXVIII** [21] (Scheme 6). The subsequent transformation sequence **XXVIII** → **XXXI** involved no essential difficulties, and the oxidation of alcohol **XXXI** with pyridinium chlorochromate (PCC) afforded ketone **VII** in a good yield.

In summary, starting from accessible initial compounds we have synthesized building blocks necessary for the assembly of target structures **II** and **III**. Coupling of this blocks and final steps of the synthesis of epothilone D isosteres will be reported elsewhere.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from thin films (neat) or Nujol mulls. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal reference. The mass spectra were obtained on a Shimadzu LCMS-2010 EV instrument; samples were introduced as solutions in ethanol. The optical rotations were measured on a Perkin Elmer 241 MS polarimeter. Analytical thin-layer chromatography was performed on Sorbfil plates (Russia). Silica gel (Lancaster, UK) was used for column chromatography.

5-{(3*S*)-4-[*tert*-Butyl(dimethyl)silyloxy]-3-methylbutanesulfonyl}-1-phenyl-1*H*-tetrazole (V). *tert*-Butyl(chloro)dimethylsilane, 1.0 g (6.6 mmol), was added at room temperature to a solution of 1.30 g (4.4 mmol) of alcohol **XVII**, 0.66 g (9.7 mmol) of imidazole, and 0.27 g (2.2 mmol) of 4-(dimethylamino)pyridine in 25 mL of methylene chloride. The mixture was stirred until the initial compound disappeared (~4 h, TLC) and evaporated, and the residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (15:1) as eluent. Yield 1.7 g (96%), colorless oily liquid, $[\alpha]_D^{20}$ = –5.4° (*c* = 1.73, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3445, 2957, 2929, 2898, 2857, 1472, 1344, 1258, 1154, 1097. ^1H NMR spectrum, δ, ppm: 0.03 s [6H, $Si(CH_3)_2$], 0.87 s (9H, *t*-Bu), 0.93 d (3H, CH_3, *J* = 7.0 Hz), 1.77–1.86 m (2H, 2-H, 3-H), 2.02–2.08 m (1H, 2-H), 3.39–3.44 m and 3.52–3.57 m (1H each, 4-H), 3.79–3.84 m (2H, CH_2SO_2), 7.57–7.69 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 3.0, 16.3 18.2, 25.6, 25.9, 34.7, 54.5, 66.6, 125.1, 129.7, 131.4, 133.1, 153.5. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 409 (16), $[M - H]^-$, 339 (84), 325 (100), 311 (64).

(3*R*)-3-[*tert*-Butyl(diphenyl)silyloxy]-5-hydroxy-4,4-dimethylpyrrolidin-2-one (VI). Camphorsulfonic acid, 0.23 g (1.0 mmol), was added at 0°C to a solution of 0.5 g (1.0 mmol) of compound **XXIV** in 40 mL of methanol–methylene chloride (1:1). The mixture was stirred until the initial compound disappeared (TLC) and treated with a saturated solution of sodium hydrogen carbonate, the organic layer was separated, the aqueous layer was extracted with diethyl ether (3×10 mL), and the extracts were combined with the organic phase, dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in methylene chloride, 0.64 g (2.0 mmol) of (diacetoxy-λ^3-iodanyl)-benzene and 0.01 g of 2,2,6,6-tetramethylpiperidine 1-oxyl were added, and the mixture was stirred at 20°C until the initial compound disappeared (TLC). The mixture was evaporated, and the residue was subjected to silica gel chromatography using petroleum ether–ethyl acetate (8:1) as eluent. Yield 0.2 g (78%), yellow oily liquid (a mixture of diastereoisomers at a ratio of 3:1). Given below are spectral data for the major stereoisomer. IR spectrum, ν, cm^{-1}: 3461, 3244, 2957, 2928, 2957, 1727, 1112, 702, 503. ^1H NMR spectrum, δ, ppm: 1.00 s (3H, CH_3), 1.06 s (3H, CH_3), 1.09 s (9H, *t*-Bu), 3.79 d (1H, C**H**OH, *J* = 10.8 Hz), 4.45 s (1H, CHOSi), 5.47 br.s (1H, NH), 7.42–7.46 m (6H, $SiPh_2$), 7.66 d (4H, $SiPh_2$, *J* = 6.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.9, 18.1, 18.4, 26.2, 43.5, 82.8, 94.4, 127.8, 130.0, 132.8, 135.9, 175.2. Mass spectrum: *m*/*z* 385 $[M + H]^+$.

2-Methyl-2-[(4*R*)-2-phenyl-1,3-dioxolan-4-yl]-pentan-3-one (VII). A solution of 0.065 g (0.3 mmol) of compound **XXXI** in 2 mL of anhydrous methylene chloride was added in one portion to a suspension of 0.05 g (0.2 mmol) of pyridinium chlorochromate in 4 mL of anhydrous methylene chloride under stirring at 0°C. The mixture was stirred for 12 h at room temperature and filtered through a thin layer of silica gel, and the sorbent was washed with methylene chloride (5×7 mL). The combined extracts were dried over $MgSO_4$ and evaporated, and the residue was purified by silica gel chromatography using ethyl acetate–petroleum ether (1:3) as eluent. Yield 0.046 g (92%), oily material (a mixture of diastereoisomers at a ratio of 3:1). ^1H NMR spectrum, δ, ppm: 1.00 s (3H, CH_3), 1.03 m (3H, CH_3, *J* = 14.9 Hz), 1.14 s (3H, CH_3), 2.63–2.69 m (2H, 3-H), 3.68–3.71 m (2H, CH_2O), 4.02 s (1H, CHO), 5.52 s (1H, C**H**Ph), 7.38–7.56 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 7.71, 18.9, 21.2, 33.1, 49.3, 66.5, 87.0, 107.2, 126.3, 127.5, 128.6, 136.1, 212.3. Mass spectrum: *m*/*z* 249 $[M + H]^+$.

(4*S*)-4-Isopropyl-5,5-dimethyloxazolidin-2-one (XI) was synthesized according to the procedure described in [19]. Colorless needles, mp 86–87°C, $[\alpha]_D^{20}$ = +26.5° (*c* = 2.62, $CHCl_3$). ^1H NMR spectrum, δ, ppm: 0.85 d and 0.94 d (3H each, CH_3, *J* = 6.4 Hz), 1.31 s and 1.41 s (3H each, CH_3), 1.72–1.79 m (1H, C**H**CH_3), 3.12 d (1H, CHN, *J* = 8.4 Hz), 7.27 br.s (1H, NH).

(4*S*)-3-(4-Bromo-1-oxobutyl)-4-isopropyl-5,5-dimethyl-1,3-oxazolidin-2-one (XII). A solution of 0.5 g (3.18 mmol) of oxazolidinone **XI** in 5 mL of THF was cooled to –80°C, 3.2 mL (6.37 mmol) of a 2 N solution of butyllithium in hexane was added under stirring, and the mixture was stirred for 15 min while slowly adding a solution of 2.4 g (12.7 mmol) of acid chloride **IX** [22] in 5 mL of THF. The mixture was stirred for 1 h, allowed to warm up to –60°C, and quenched by slowly adding 0.5 mL of aqueous THF. The mixture was then adjusted to room temperature and treated with a saturated solution of ammonium chloride, the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2×10 mL). The extracts were combined with the organic phase, dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by silica gel column chromatography using ethyl acetate–petroleum ether (1:3) as eluent. Yield 0.5 g (81%), yellow viscous liquid. $[\alpha]_D^{20}$ = +29.3° (*c* = 3.94, CH_2Cl_2). IR spectrum, ν,

cm^{-1}: 2971, 2933, 2880, 1774, 1701. ^1H NMR spectrum, δ, ppm: 0.94 d and 1.01 d (3H each, CH_3, J = 7.0 Hz), 1.38 s and 1.50 s (3H each, CH_3), 2.11–2.15 m (1H, CH), 2.20–2.25 m (2H, 3′-H), 3.05–3.18 m (2H, 2′-H), 3.49 t (2H, 4′-H, J = 6.7 Hz), 4.13 d (1H, 4-H, J = 3.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 17.1, 21.4, 21.6, 27.3, 28.9, 29.6, 32.7, 33.9, 66.4, 83.0, 153.5, 172.5. Mass spectrum, m/z (I_{rel}, %): 307 (20) $[M + H]^+$, 227 (100).

(4*S*)-4-Isopropyl-5,5-dimethyl-3-[1-oxo-4-(1-phenyl-1*H*-tetrazole-5-sulfonyl)butyl]-1,3-oxazolidin-2-one (XIV). Compound **XIII**, 0.06 g (0.34 mmol), was dissolved in 5 mL of acetone, 0.06 g (0.6 mmol) of sodium carbonate was added under stirring, the mixture was stirred for 10 min, and a solution of 0.08 g (0.26 mmol) of bromide **XII** in 2 mL of acetone was slowly added. The mixture was stirred for 12 h, filtered, and evaporated, and the residue was purified by silica gel column chromatography using ethyl acetate–petroleum ether (1:3) as eluent. Yield 0.1 g (86%), colorless viscous liquid, $[\alpha]_D^{20}$ = +21.8° (c = 2.49, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 2976, 2934, 2879, 1768, 1736, 1701. ^1H NMR spectrum, δ, ppm: 0.93 d and 1.01 d (3H each, CH_3, J = 7.0 Hz), 1.38 s and 1.50 s (3H each, CH_3), 2.11–2.15 m (1H, CH), 2.21–2.26 m (2H, 3′-H), 3.05–3.18 m (2H, 2′-H), 3.47–3.50 m (2H, 4′-H), 4.13 d (1H, 4-H, J = 3.1 Hz), 7.53–7.57 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 17.0, 21.4, 23.9, 28.8, 29.5, 32.4, 34.0, 66.3, 83.0, 123.9, 129.8, 130.1, 133.6, 153.5, 154.1, 172.4. Mass spectrum: m/z 404 $[M + H]^+$.

(4*S*,2′*S*)-4-Isopropyl-5,5-dimethyl-3-[2-methyl-1-oxo-4-(1-phenyl-1*H*-tetrazole-5-sulfonyl)butyl]-1,3-oxazolidin-2-one (XV). A solution of 0.1 g (0.25 mmol) of compound **XIV** in 5 mL of THF was cooled to –78°C, 0.5 mL (0.5 mmol) of a 1 M solution of hexamethyldisilazane sodium salt in THF was added dropwise under stirring, the mixture was stirred for 30 min, and 0.15 mL (2.5 mmol) of methyl iodide was added. The mixture was stirred for 1 h at –78°C and for 12 h at –30°C, a saturated solution of ammonium chloride was added, the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by silica gel column chromatography using ethyl acetate–petroleum ether (1:5) as eluent. Yield 0.09 g (89%), colorless viscous liquid, $[\alpha]_D^{20}$ = +37.8° (c = 1.95, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 2971, 2931, 2878, 2853, 1772, 1730, 1698. ^1H NMR spectrum, δ, ppm: 0.92 d and 0.98 d (3H each, CH_3, J = 7.0 Hz), 1.31 d (3H, CH_3, J = 6.7 Hz), 1.36 s and 1.48 s (3H each, CH_3), 1.89–1.94 m (1H, 3′-H), 2.11–2.15 m (1H, CH), 2.29–2.33 m (1H, 3′-H), 3.34–3.37 m and 3.43–3.48 m (1H each, 4′-H), 3.88–3.91 m (1H, 2′-H), 4.17 d (1H, 4-H, J = 3.1 Hz), 7.51–7.55 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 16.9, 18.5, 21.4, 21.6, 28.8, 29.6, 31.0, 31.9, 37.1, 66.1, 82.8, 124.0, 129.8, 130.2, 133.7, 153.0, 154.5, 176.4. Mass spectrum: m/z 418 $[M + H]^+$.

(2*S*)-2-Methyl-4-(1-phenyl-1*H*-tetrazole-5-sulfonyl)butan-1-ol (XVI). A solution of 0.022 g (0.58 mmol) of $LiAlH_4$ in THF was added dropwise under stirring at ~5°C to a solution of 0.2 g (0.48 mmol) of compound **XV** in 5 mL of THF. The mixture was stirred for 2 h at room temperature, aqueous THF (1:1) was added, the mixture was stirred for 5 min at ~5°C, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue, 0.11 g (89%), was a yellow viscous liquid which was used in further synthesis without chromatographic purification.

(2*S*)-2-Methyl-4-(1-phenyl-1*H*-tetrazole-5-sulfonyl)butan-1-ol (XVII). A solution of 0.05 g (0.04 mmol) of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 0.4 mL of 47% hydrogen peroxide was added dropwise under stirring at ~0°C to a solution of 0.05 g (0.19 mmol) of compound **XVI** in 3 mL of ethanol. The mixture was stirred for 12 h at room temperature and treated with brine, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue, 0.05 g (85%), was a light yellow viscous liquid which was used in further synthesis without chromatographic purification.

(4*R*)-5,5-Dimethyl-2-phenyl-1,3-dioxane-4-carboxamide (XIX). Compound **XVIII** [23], 0.06 g (0.41 mmol), was dissolved in 5 mL of benzene, 0.09 mL (0.62 mmol) of (dimethoxymethyl)benzene and a catalytic amount of *p*-toluenesulfonic acid were added, and the mixture was stirred for 30 min at room temperature, and evaporated. The residue was subjected to silica gel column chromatography using petroleum ether–ethyl acetate as eluent to isolate 0.07 g (70%) of oily acetal **XIX** as a 10:1 mixture of diastereoisomers with respect to the acetal chiral center.

Major (2*R*,4*R*)-isomer. IR spectrum, ν, cm^{-1}: 3486, 3290, 3207, 2957, 2931, 2895, 2858, 1691. ^1H NMR spectrum, δ, ppm: 1.12 s and 1.21 s (3H each, CH_3), 3.70 d and 3.75 d (1H each, CH_2, J = 11.6 Hz), 4.13 s

(1H, CHO), 5.54 s (1H, C**H**Ph), 5.62 br.s and 6.46 br.s (1H each, NH_2), 7.40–7.52 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 19.2, 21.8, 33.1, 78.5, 84.0, 101.4, 126.2, 128.4, 129.3, 137.8. 171.8. Mass spectrum: *m*/*z* 236 $[M + H]^+$.

(1*R*)-1-Amino-4-methoxy-3,3-dimethyl-1,4-dioxobutan-2-yl benzoate (XXI). Compound **XIX**, 0.37 g (0.15 mmol), was dissolved in a mixture of 30 mL of acetonitrile, 30 mL of carbon tetrachloride, and 15 mL of water, 0.04 g (0.15 mmol) of $RuCl_3 \cdot H_2O$ and 1.6 g (7.5 mmol) of $NaIO_4$ were added in succession, and the mixture was stirred for 4 h at room temperature. The mixture was then diluted with an equal volume of water, the organic phase was separated, the aqueous phase was extracted with ethyl acetate (3×100 mL), and the extracts were combined with the organic phase, dried over Na_2SO_4, filtered, and evaporated to isolate 0.37 g (92%) of acid **XX** as an oily liquid which was subjected to methylation without additional purification.

Acid **XX**, 0.2 g (0.8 mmol), was dissolved in 10 mL of diethyl ether, 0.07 mL (1.6 mmol) of a diazomethane solution was added at room temperature, and the mixture was stirred until the initial compound disappeared (TLC). The mixture was evaporated, and the residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (3:1) as eluent. Yield of ester **XXI** 0.21 g (93%), colorless oily liquid, $[\alpha]_D^{20}$ = +18.2° (*c* = 0.68, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3491, 3292, 3210, 2956, 2931, 2895, 2851, 1689. ^1H NMR spectrum, δ, ppm: 1.35 s and 1.38 s (3H each, CH_3), 3.69 s (3H, OCH_3), 5.73 br.s (1H, CHO), 6.11 br.s (2H, NH_2), 7.46–7.61 m (3H, Ph), 8.06 d (2H, Ph, *J* = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 22.2, 23.5, 41.4, 55.7, 83.0, 128.1, 129.2, 129.9, 134.2, 161.7, 171.2, 173.2. Mass spectrum: *m*/*z* 280 $[M + H]^+$.

(2*R*)-4-[*tert*-Butyl(dimethyl)silyloxy]-2-hydroxy-3,3-dimethylbutanamide (XXIII). *tert*-Butyl(chloro)dimethylsilane, 0.1 g (0.68 mmol), was added at room temperature to a solution of 0.1 g (0.68 mmol) of compound **XVIII**, 0.15 g (2.18 mmol) of imidazole, and 0.04 g (0.34 mmol) of DMAP in 15 mL of methylene chloride. The mixture was stirred until the initial compound disappeared (~4 h, TLC) and evaporated, and the residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (3:1) as eluent. Yield 0.17 g (94%), colorless oily liquid, $[\alpha]_D^{20}$ = +29.7° (*c* = 2.00, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3478, 3397, 3350, 3319, 2954, 2930, 2859, 1667, 1096, 837. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.08 s [6H, $Si(CH_3)_2$], 0.90 s (9H, *t*-Bu), 0.94 s and 1.02 s (3H each, CH_3), 3.48 d and 3.58 d (1H each, CH_2, *J* = 11.6 Hz), 4.02 s (1H, C**H**OH), 5.94 br.s and 6.80 br.s (1H each, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 5.7, 18.1, 20.0, 21.4, 25.7, 38.3, 73.1, 78.8, 175.2. Mass spectrum, *m*/*z* (I_{rel}, %): 284 (100), 262 (60) $[M + H]^+$.

(2*R*)-4-[*tert*-Butyl(dimethyl)silyloxy]-2-[*tert*-butyl(diphenyl)silyloxy]-3,3-dimethylbutanamide (XXIV). *tert*-Butyl(chloro)diphenylsilane, 0.6 g (2.2 mmol), was added at room temperature to a solution of 0.52 g (1.99 mmol) of compound **XXIII**, 0.43 g (6.4 mmol) of imidazole, and 0.12 g (0.99 mmol) of DMAP in 20 mL of methylene chloride. The mixture was stirred until the initial compound disappeared (~4 h, TLC) and evaporated, and the residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (3:1) as eluent. Yield 0.92 g (92%), colorless oily liquid, $[\alpha]_D^{20}$ = +7.7° (*c* = 1.93, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3486, 3290, 3207, 2957, 2931, 2858, 1691, 1112, 838, 702. ^1H NMR spectrum, δ, ppm: 0.05 s [6H, $Si(CH_3)_2$], 0.83 s (9H, *t*-Bu), 0.86 s and 0.89 s (3H each, CH_3), 1.12 s (9H, *t*-Bu), 3.23 d and 3.41 d (1H each, CH_2, *J* = 11.6 Hz), 4.14 s (1H, CHO), 5.56 br.s and 6.10 br.s (1H each, NH_2), 7.34–7.41 m (6H, $SiPh_2$) 7.65–7.70 m (4H, $SiPh_2$). ^{13}C NMR spectrum, δ_C, ppm: 5.53, 18.2, 18.3, 19.7, 20.8, 25.9, 27.2, 40.3, 69.1, 79.0, 127.7, 130.0, 132.9, 135.9, 174.3. Mass spectrum: *m*/*z* 501 $[M + H]^+$.

3-[*tert*-Butyl(diphenyl)silyloxy]-4,4-dimethyldihydrofuran-2(3*H*)-one (XXVI). Di-*tert*-butyl dicarbonate, 0.22 g (0.98 mmol), was added at room temperature to a solution of 0.38 g (0.76 mmol) of amide **XXIV** and 0.10 g (0.84 mmol) of DMAP in 20 mL of acetonitrile. The mixture was stirred until the initial compound disappeared (TLC) and evaporated. The residue was 0.43 g (93%) of oily carbamate **XXV**. It was subjected to hydrolysis without purification.

A solution of 0.4 g (0.67 mmol) of compound **XXV** in 20 mL of methanol–methylene chloride (1:1) was cooled to 0°C, 0.15 g (0.67 mmol) of camphorsulfonic acid was added, and the mixture was stirred until the initial compound disappeared (TLC). The mixture was treated with a saturated solution of sodium hydrogen carbonate, the organic phase was separated, the aqueous phase was extracted with diethyl ether (3×10 mL), the extracts were combined with the organic phase, dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by silica gel chromatography on silica gel using petroleum ether–ethyl acetate (20:1) as

eluent. Yield 0.17 g (68%), light yellow viscous liquid, $[\alpha]_D^{20}$ = +12.3° (*c* = 0.84, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 2957, 2928, 2857, 1719, 1112, 703. ^1H NMR spectrum, δ, ppm: 0.74 s and 1.13 s (3H each, CH_3), 1.15 s (9H, *t*-Bu), 3.70 d and 3.89 d (1H each, CH_2, *J* = 8.8 Hz), 4.04 s (1H, CHOSi), 7.37–7.43 m (6H, $SiPh_2$), 7.73 d.d (4H, $SiPh_2$, *J* = 6.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.2, 21.3, 22.9, 27.0, 42.1, 79.3, 89.5, 127.9, 129.0, 131.8, 135.8, 177.2. Mass spectrum: *m*/*z* 370 $[M + H]^+$.

(4*R*)-4-[*tert*-Butyl(diphenyl)silyloxy]-3,3-dimethylpyrrolidine-2,5-dione (XXVII). A solution of 0.2 g (0.5 mmol) of compound **VI** in 2 mL of anhydrous methylene chloride was added in one portion under stirring at 0°C to a suspension of 0.14 g (0.75 mmol) of pyridinium dichromate in 4 mL of anhydrous methylene chloride. The mixture was stirred for 12 h at room temperature and filtered through a thin layer of silica gel, the precipitate was washed on a filter with methylene chloride (5×7 mL), the washings were combined, dried over $MgSO_4$, and evaporated, and the residue was subjected to silica gel chromatography using ethyl acetate–petroleum ether (1:3) as eluent. Yield 0.14 g (71%), oily material, $[\alpha]_D^{20}$ = +28.3° (*c* = 0.51, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3244, 2957, 2928, 2857, 1727, 1112, 702, 503. ^1H NMR spectrum, δ, ppm: 0.82 s (3H, CH_3), 1.14 s (9H, *t*-Bu), 1.24 s (3H, CH_3), 4.29 s (1H, CHOSi), 7.37–7.46 m (6H, $SiPh_2$), 7.71 d.d and 7.80 d.d (2H each, $SiPh_2$, *J* = 6.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.8, 21.2, 26.9, 29.7, 47.3, 77.7, 127.6, 130.1, 132.6, 136.3, 174.9, 180.1. Mass spectrum: *m*/*z* 383 $[M + H]^+$.

(2*R*)-3,3-Dimethylbutane-1,2,4-triol (XXVIII). A solution of 2.70 g (15.7 mmol) of (*R*)-(–)-pantolactone in 10 mL of THF was added dropwise under stirring at 0°C to a suspension of 0.9 g (23.62 mmol) of $LiAlH_4$ in 30 mL of anhydrous THF. The mixture was stirred for 4 h at room temperature, anhydrous Na_2SO_4 was added, and 50% sulfuric acid was slowly added to pH ~3. The mixture was stirred for 30 min and neutralized by adding anhydrous sodium hydrogen carbonate, the precipitate was filtered off and washed on a filter with ethyl acetate (5×20 mL), the filtrate was evaporated, and the residue was dried under reduced pressure on heating on a water bath. Yield 2.4 g (88%), colorless oily liquid, $[\alpha]_D^{20}$ = –15.85° (*c* = 0.1, MeOH). IR spectrum, ν, cm^{-1}: 3368, 3176, 3120, 1460, 1376, 1184, 1144, 1128, 1036, 1008, 816. Found, %: C 53.56; H 10.20. $C_6H_{14}O_3$. Calculated, %: C 53.73; H 10.44.

2-Methyl-2-[(4*R*)-2-phenyl-1,3-dioxolan-4-yl]-propan-1-ol (XXIX). Compound **XXVIII**, 0.6 g (4.5 mmol), was dissolved in 10 mL of benzene, 1.03 g (6.75 mmol) of (dimethoxymethyl)benzene and a catalytic amount of *p*-toluenesulfonic acid were added, and the mixture was stirred for 2 h at room temperature. The mixture was evaporated, and the residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (3:1) as eluent. Yield 0.94 g (94%), oily substance (a mixture of diastereoisomers at a ratio of 3:1). IR spectrum, ν, cm^{-1}: 3300, 1670, 1465, 1380, 1280. ^1H NMR spectrum, δ, ppm: 0.84 s and 0.88 s (3H each, CH_3), 3.41 d and 3.43 d (1H each, 1-H, *J* = 11.0 Hz), 3.52 d and 3.71 d (1H each, 5-H, *J* = 7.3 Hz), 3.75–3.78 m (1H, 4-H), 5.49 s (1H, C**H**Ph), 7.35–7.50 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 21.8, 23.9, 35.3, 64.5, 68.9, 85.7, 104.3, 126.8, 127.9, 128.5, 136.1. Mass spectrum: *m*/*z* 223 $[M + H]^+$.

2-Methyl-2-[(4*R*)-2-phenyl-1,3-dioxolan-4-yl]-propanal (XXX). A solution of 0.51 g (1.35 mmol) of compound **XIX** in 2 mL of anhydrous methylene chloride was added in one portion to a suspension of 0.2 g (0.9 mmol) of pyridinium dichromate in 4 mL of anhydrous methylene chloride under stirring at 0°C. The mixture was stirred for 12 h at room temperature and filtered through a thin layer of silica gel, the precipitate was washed on a filter with methylene chloride (5×7 mL), and the combined washings were dried over $MgSO_4$ and evaporated. The residue was purified by silica gel chromatography using ethyl acetate–petroleum ether (1:3) as eluent. Yield 0.13 g (67%), oily material (a mixture of diastereoisomers at a ratio of 3:1). IR spectrum, ν, cm^{-1}: 1730, 1480, 1390, 1270, 1235, 1070. ^1H NMR spectrum, δ, ppm: 1.03 s and 1.26 s (3H each, CH_3), 3.71 d and 3.74 d (1H each, 5-H, *J* = 7.3 Hz), 3.95–3.97 m (1H, 4-H), 5.56 s (1H, C**H**Ph), 7.35–7.60 m (5H, Ph), 9.68 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 17.1, 18.3, 48.4, 65.4, 85.1, 105.6, 127.9, 128.1, 128.6, 137.2, 203.6. Mass spectrum: *m*/*z* 221 $[M + H]^+$.

2-Methyl-2-[(4*R*)-2-phenyl-1,3-dioxolan-4-yl]-pentan-3-ol (XXXI). A solution of 0.09 g (0.41 mmol) of compound **XXX** in 10 mL of diethyl ether was cooled to –78°C, a solution of ethylmagnesium bromide prepared from 0.1 g of magnesium turnings and 0.3 mL of ethyl bromide in 1 mL of diethyl ether was slowly added under stirring, and the mixture was stirred for 1 h and hydrolyzed with a saturated aqueous solution of ammonium chloride. The organic phase was separated, the aqueous phase was extracted with

ethyl acetate (3×40 mL), the combined extracts were dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (2:1) as eluent. Yield 0.09 g (87%), oily material (a mixture of diastereoisomers with respect to C*HOH at a ratio of 2:1). IR spectrum, ν, cm^{-1}: 3321, 1478, 1385, 1270, 1235, 1070. ^{1}H NMR spectrum, δ, ppm: 0.86 s (3H, CH_3), 1.00 t (3H, CH_3, J = 14.9 Hz), 1.29 s (3H, CH_3), 1.54–1.66 m (2H, 3-H), 3.43–3.44 m (1H, 2-H), 3.61 d (1H, CH_2O, J = 7.3 Hz), 3.63–3.69 m (1H, CHO), 3.71 d (1H, CH_2O, J = 7.3 Hz), 5.56 s (1H, C**H**Ph), 7.34–7.53 m (5H, Ph). Mass spectrum, m/z (I_{rel}, %): 505 (21) $[M + H]^+$, 475 (100).

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