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Synthesis of 2,2-functionalized benzo[1,3]dioxoles

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ABSTRACT

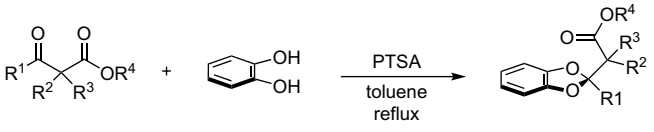
Highly functionalized catechol ketals exhibiting either a *tert*-butyl moiety or a spiro center in position 2 are synthesized by ketalization and functionalized in a sequence of subsequent transformations. By a specific ketalization protocol catechol ketals of enolizable β-keto esters can be prepared. With the succeeding steps these compounds incorporate moieties, which are not compatible and accessible by direct ketalization of catechol.

1. Introduction

Benzo[1,3]dioxoles with *tert*-butyl substituent in position 2 play an important role as planar, π-rich, and rigid building blocks.[1] Furthermore, for the determination of attached stereo centers using enantiomerically pure 2-*tert*-butyl-2-methylbenzo[1,3]dioxole carboxylic acid has found significant attention.[2] These architectures can also be exploited for fluorescent sensors.[3] More recently, functionalized catechol ketals have found application in the synthesis of triphenylene ketals by oxidative trimerization.[4] By this synthetic pathway using $MoCl_5$ or anodic protocols, the first artificial caffeine receptors were established.[5] Such unique platforms starting from catechol ketals gave rise to a variety of novel effects[6] and sensor applications.[7] The rigid nature of the ketal unit in the 2,2-disubstituted benzo[1,3]dioxole is crucial for a powerful application later on.[8] Spiro ketals or ketals exhibiting a *tert*-butyl moiety lead to a well defined arrangement of functional groups. The installation of substituents in position 2 of the benzo[1,3]dioxole can be achieved by electrophilic displacement of a chloro moiety by ketene acetals.[9] The more common synthetic pathway exploits the condensation with catechol under acidic conditions using sulfonic acids or their metal salts.[10] For good conversions either the formed water is continuously removed or dehydrating agents are applied.[11] Since those reaction conditions are harsh the synthesis of appropriately functionalized catechol ketals remains still a significant issue.[12] In particular, *tert*-butyl groups adjacent to carbonyl of the ketone require specific reaction conditions in order to perform the transformation successfully. We report the preparation of variety of differently substituted benzo[1,3]dioxoles in the ketal moiety.

2. Results and discussion

The synthesis of catechol ketals commenced with the transformation of a β-keto ester with 1.5 equiv of catechol in the presence of maximum 0.1 equiv of *p*-toluenesulfonic acid in toluene (Scheme 1) using a Dean–Stark trap. Some of these β-keto esters were commercially available and others have been prepared by alkylation of the corresponding β-keto esters.



Scheme 1.

The yields of the obtained catechol ketals were strongly dependent on the nature of the β-keto ester. Especially when steric hindrance is involved catechol ketals do not form easily. Therefore, thermal activation is required. Shifting of the ketalization equilibrium by removal of water is for acceptable yields necessary. Enolizable ketones (Table 1, entries 1, 2, 8, and 9) are under these conditions prone to decarboxylation and lead carbonyl components with lost functionality for later application and more important, they exhibit a less sterically demanding environment. Consequently, a significant byproduct is the benzodioxole derived from

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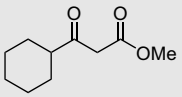
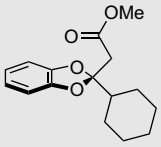
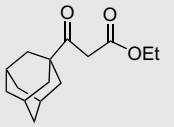
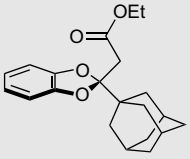
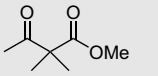
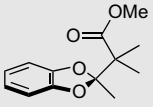
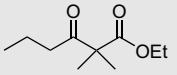
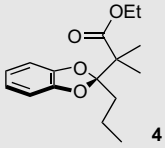
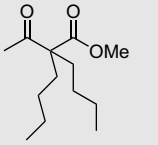
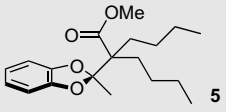
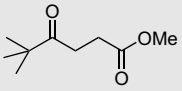
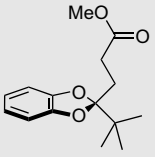
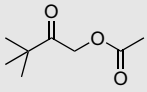
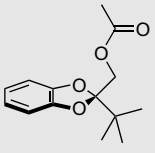
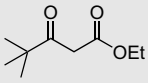
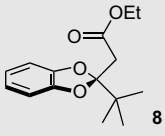
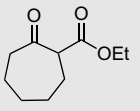
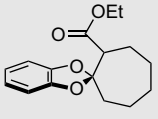
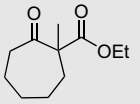
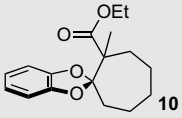
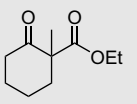
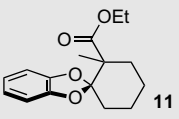
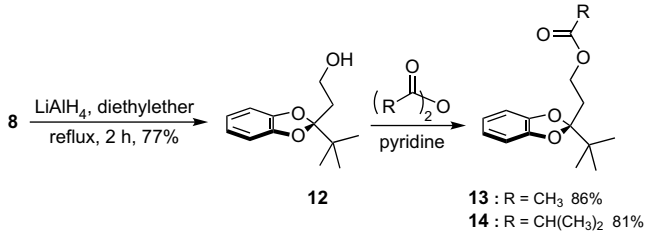
Table 1
Ketalization of enolizable and non-enolizable β-keto esters

Entry	Starting material	Ketal	Yield
1		 **1**	29%
2		 **2**	23%
3		 **3**	70%
4		 **4**	65%
5		 **5**	64%
6		 **6**	46%
7		 **7**	38%
8		 **8**	38%
9		 **9**	35%
10		 **10**	70%
11		 **11**	72%

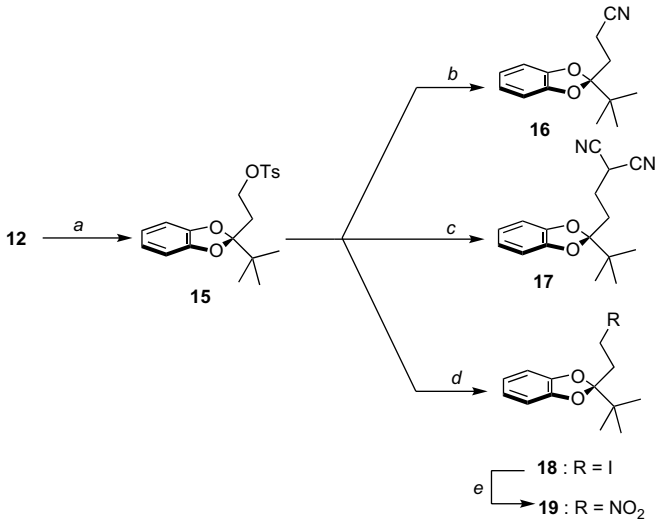
the decarboxylated intermediate. When all reagents are added at once (e.g., for **8**) and the mixture is subsequently heated to reflux, only traces of catechol ketals are detected. Cyclodehydration of 1,4-dicarbonyl compounds is another side reaction that competes with the ketalization process (Table 1, entry 5). To maximize the yield of the desired highly functionalized catechol ketals, the β-keto ester was added drop by drop over a period of 8–12 h to the vigorously boiling reaction mixture. Continuous removal of water was performed by a Dean–Stark apparatus. This protocol gave access to 23–38% isolated yield. Application of other ketalization methods involving dehydrating agents gave inferior yields. Non-enolizable substrates rendered significantly higher yields (entries 3–5, 10, 11). All catechol ketals form colorless oils that are purified by distillation or by chromatography on silica.

In particular compound **8** is of specific interest for receptor applications.[8] Consequently, more attention was given to the conversion of this intermediate. Treatment of catechol ketal **8** with lithium aluminum hydride in ether under reflux conditions for 3 h gave rise to the corresponding alcohol **12** in 77% yield.[13] Subsequently, **12** was allowed to react with acetic anhydride or isobutyric acid anhydride in the presence of pyridine as a solvent to afford **13** and **14**, respectively (Scheme 2).



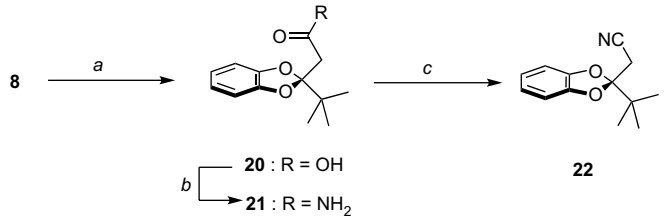
Scheme 2.

The preparation of tosylate derivative **15** by treatment of **12** with *p*-toluenesulfonyl chloride and pyridine,[14] appeared to be a practical starting point for the elaboration into compounds **16**, **17**, **18**, and **19** (Scheme 3). The introduction of an additional carbon atom was achieved by nucleophilic substitution using cyanide anions providing **16** in very good yield.[14] The versatile tosylate derivative **15** opens up by nucleophilic displacement a variety of functionalized benzodioxoles as, e.g., the geminal dicyano derivative **17** by nucleophilic substitution using malonitrile under basic conditions. For an efficient installation of a nitro moiety a prior exchange to the better leaving group iodide had to be made under typical Finkelstein conditions.[15] The tosylate derivative **15** was converted to the nitro compound **19** in two steps.[16] Thus, iodination of **15** by sodium iodide in acetone is followed by nitration using sodium nitrite in DMF. The resulting nitro compound **19** was obtained in good yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) TsCl, pyridine, overnight, rt, 80%; (b) NaCN, DMSO, 80 °C, 3 h, 84%; (c) malononitrile, K_2CO_3, DMF, 80 °C, 4 h, 42%; (d) NaI, acetone, reflux, 24 h, 81%; (e) $NaNO_2$, DMF, rt, 5 h, 48%.

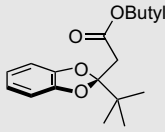
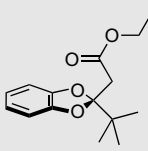
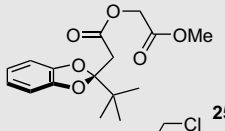
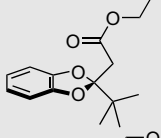
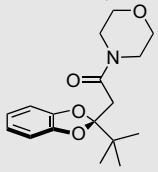
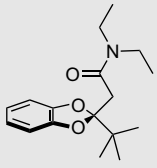
Catechol ketal **8** was converted into nitrile **22** in three steps: hydrolysis of the ester **8** with LiOH in THF/H_2O to the acid **20**,[17] conversion of the acid to the carboxamide **21**, and dehydration of this carboxamide to give nitrile **22** in 88% yield. The dehydration step was carried out with *p*-toluenesulfonyl chloride in pyridine.[18] Other reaction conditions for dehydration of carboxamide including Martin's sulfurane,[19] failed completely since either no reaction was observed or the benzo moiety was attacked by electrophilic side reactions (Scheme 4).



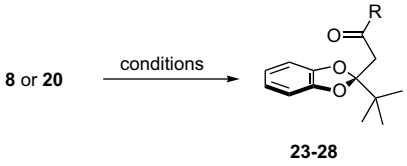
Scheme 4. Reagents and conditions: (a) LiOH, THF, H_2O, 4 days, rt, 95%; (b) NH_4OH, DCC, DMAP, CH_2Cl_2, rt, overnight, 68%; (c) TsCl, pyridine, rt, overnight, 88%.

Furthermore, the carboxylic acid **20** is a key intermediate, which gave rise to a variety of compounds by alkylation or DCC coupling. Alternatively, direct displacement of the ester **8** can be exploited as well. The obtained compounds **23**–**28** are not accessible by direct ketalization with catechol. Thus, alkylation of catechol ketal **20** with *n*-butyliodide, methyl bromoacetate, or 1,2-dichloroethane afforded **23**, **25**, and **26**, respectively. Whereas DCC coupling of **20** with ethylene glycol monomethylether or diethylamine afforded **24** and **28**, respectively. And finally, the treatment of catechol ketal **8** with morpholine at reflux conditions for 48 h gave **27** in satisfactory yield (Table 2).

Table 2
Results of Scheme 5

Nr.	Starting material	Product	Yield
1	**20**	 **23**	86%[a]
2	**20**	 **24**	84%[b]
3	**20**	 **25**	89%[a]
4	**20**	 **26**	59%[a]
5	**8**	 **27**	70%[c]
6	**8**	 **28**	55%[b]

[a] via alkylation with NaH and suitable alkylation means in DMF.
[b] Conversion with DCC, DMAP, and suitable amine or alcohol.
[c] Conversion of ketal **8** in boiling morpholine.



Scheme 5.

3. Conclusion

Benzo[1,3]dioxoles with substituents in position 2 are well accessible by ketalization of the carbonyl precursor using catechol. When bulky moieties like *tert*-butyl groups are installed in position 2 of the heterocycle, decarboxylative degradation of the β-keto ester is a severe side reaction. Slow addition of the reaction partner circumvents this particular challenge. For the introduction of other functional groups subsequent conversions have to be applied. The carboxylate **8** turned out to be a readily available and versatile intermediate for a variety of 2,2-functionalized catechol ketals. Subsequent transformations allow the installation of nitro, cyano, iodo, chloro, amido, and many other moieties at the side chain, which are not compatible with direct ketalization. These building blocks represent not only valuable key precursors for receptors based on triphenylene ketals but also might have their place in other areas of molecular sciences.

4. Experimental

4.1. General

All reagents were used in analytical grade. Solvents were desiccated if necessary by standard methods. Column chromatography was performed on silica gel (particle size 63–200 μm, Merck, Darmstadt, Germany) using mixtures of cyclohexane with ethylacetate as eluents. Melting points were determined on a Melting Point Apparatus SMP3 (Stuart Scientific, Watford Herts, UK) and were uncorrected. Micro analyses were performed using a Vario EL III (Elementar-Analysensysteme, Hanau, Germany). ^{1}H NMR spectra were recorded at 25 °C on a Bruker DPX 300 or DPX 400 (Analytische Messtechnik, Karlsruhe, Germany). Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as internal standard or traces of $CHCl_3$ in the deuterated solvent. Mass spectra were obtained on a MAT8200, MAT95XL (Finnigan, Bremen, Germany), MS50 (Kratos, Manchester, England) or FT-ICR (Bruker APEX IV) employing EI, ESI, and HRMS.

4.1.1. General procedure for ketalization of enolizable β-keto esters

In a 500 mL two-necked flask, catechol (1.5 equiv) was dissolved in 250 mL toluene. After addition of *p*-toluenesulfonic acid monohydrate (0.1 equiv) the mixture was heated to vigorous reflux at a Dean–Stark apparatus for about 2 h. Then, a solution of the β-keto ester in dry toluene (100 mL) was added in 10 mL portions slowly over a period of 10 h by using dropping funnel. The mixture was heated under reflux overnight; H_2O was collected by a Dean–Stark trap. After concentration, the resulting oil was fractionated with *t*-BuOMe (400 mL) and 3% NaOH soln (200 mL). The organic layer was washed with H_2O (5×200 mL) and brine (200 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. Upon distillation of the crude product, the ketal product was obtained.

4.1.2. General procedure for ketalization of non-enolizable β-keto ester

In a 500 mL two-necked flask, the β-keto ester was dissolved in toluene (250 mL). After addition of catechol (1.5 equiv) and *p*-toluenesulfonic acid monohydrate (0.1 equiv), the mixture was heated under reflux overnight; H_2O was collected by a Dean–Stark trap. After concentration, the resulting oil was fractionated with *t*-BuOMe (400 mL) and 3% NaOH soln (200 mL). The organic layer was washed several times with H_2O (5×200 mL) and brine (200 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. Upon distillation of the crude product, the ketal product was obtained.

4.2. 2-Cyclohexyl-2(methoxycarbonylmethyl)benzo[1,3]-dioxole (1)

Upon distillation of the crude product (101 °C, 5.4×10^{-2} mbar), the ketal product (1.5 g, 29%) was obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.06–1.33 (m, 5H), 1.63–1.91 (m, 5H), 2.04–2.14 (m, 1H), 2.94 (s, 2H), 3.60 (s, 3H), 6.73–6.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.80, 25.93, 25.97, 40.26, 45.06, 51.82, 108.03, 118.59, 121.12, 147.53, 168.85; MS (EI): *m*/*z* (%)=276.2 (80) $[M]^{\bullet+}$. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.93; H, 7.44.

4.3. 2-(1-Adamantyl)-2-(ethoxycarbonylmethyl)-benzo[1,3]dioxole (2)

The crude product was chromatographed using cyclohexane–ethylacetate (9:1) as eluent and the ketal product (1.8 g, 23%) was obtained as a colorless solid. Mp 76–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, *J*=7.2 Hz, 3H), 1.63–1.74 (m, 12H), 1.99–2.04 (m, 3H), 2.94 (s, 2H), 3.88 (q, *J*=7.2 Hz, 2H), 6.70–6.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.55, 27.85, 35.26, 36.65, 38.60, 42.29, 60.75, 107.22, 120.09, 120.80, 148.62, 168.98; MS (EI): *m*/*z* (%)=342.2 (35) $[M]^{\bullet+}$. Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.81; H, 7.73.

4.4. 2-(2,2-Dimethyl acetic acid methylester)-2-methyl-benzo[1,3]dioxole (3)

Upon distillation of the crude product (74 °C, 2.7×10^{-2} mbar), the ketal product (12.6 g, 70%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 6H), 1.68 (s, 3H), 3.68 (s, 3H), 6.77 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.55, 21.30, 51.03, 52.12, 108.15, 119.73, 121.06, 147.44, 174.38; MS (ES^+): *m*/*z*=259.1 $[M+Na^+]$. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.94; H, 6.91.

4.5. 2-(1-Ethoxycarbonyl-1-(methyl)-ethyl)-2-propyl-benzo[1,3]dioxole (4)

Upon distillation of the crude product (98 °C, 10^{-2} mbar), the ketal (17.7 g, 65%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, *J*=7.40 Hz, 3H), 1.18 (t, *J*=7.10 Hz, 3H), 1.32 (s, 6H), 1.34–1.44 (m, 2H), 2.00–2.04 (m, 2H), 4.09 (q, *J*=7.10 Hz, 2H), 6.70–6.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.91, 14.00, 15.10, 20.58, 37.16, 51.69, 60.89, 107.17, 120.79, 120.85, 148.78, 174.01; MS (ES^+): *m*/*z*=301.2 $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{16}H_{22}NaO_4$ $[M+Na]^+$ 301.1410, found 301.1403.

4.6. 2-(1-Butyl)-1-(methoxycarbonyl)pentyl-2-methyl-benzo[1,3]dioxole (5)

The crude product was chromatographed using cyclohexane–ethylacetate (9:1) as eluent, and the ketal (3.1 g, 64%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, *J*=7.1 Hz, 6H), 1.17–1.43 (m, 8H), 1.64 (s, 3H), 1.76–1.88 (m, 4H), 3.63 (s, 3H), 6.73–6.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.94, 22.26, 23.52, 26.82, 30.84, 51.77, 57.70, 108.21, 120.41, 120.98, 147.22, 173.57; MS (EI): *m*/*z* (%)=320.2 (5) $[M]^{\bullet+}$; HRMS: *m*/*z* calcd for $C_{19}H_{28}NaO_4$ $[M+Na^+]$ 343.1880, found 343.1871.

4.7. 2-(1,1-Dimethylethyl)-2-(2-methoxycarbonylethyl)-benzo[1,3]dioxole (6)

Upon distillation of the crude product (195 °C, 10^{-5} mbar), the ketal (0.69 g, 46%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.04 (s, 9H), 2.43–2.37 (m, 4H), 3.62 (s, 3H), 6.70–6.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.37, 27.27, 29.35, 40.37, 51.61, 107.12, 120.84, 122.88, 148.81, 173.79; MS (EI, 70 eV): *m*/*z* (%)=264.1 (18) $[M]^{\bullet+}$; HRMS: *m*/*z* calcd for $C_{15}H_{20}O_4$ $[M]^+$ 264.1362, found 264.1363.

4.8. 2-(Acetoxymethyl)-2-(1,1-dimethylethyl)-benzo[1,3]dioxole (7)

Upon distillation of the crude product (117 °C, 10^{-5} mbar), the ketal (1.70 g, 38%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.09 (s, 9H), 1.82 (s, 3H), 4.48 (s, 2H), 6.75 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.43, 24.39, 38.68, 63.59, 107.24, 119.88, 120.86, 148.62, 170.54; MS (EI, 70 eV): *m*/*z* (%)=250.1 (26) $[M]^{\bullet+}$; HRMS: *m*/*z* calcd for $C_{14}H_{18}O_4$ $[M]^+$ 250.1205, found 250.1207.

4.9. 2-(1,1-Dimethylethyl)-2-(ethoxycarbonylmethyl)-benzo[1,3]dioxole (8)

Upon distillation of the crude product (101 °C, 1.3×10^{-2} mbar), the ketal (26 g, 38%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, *J*=7.20 Hz, 3H), 1.07 (s, 9H), 2.96 (s, 2H), 3.88 (q, *J*=7.20 Hz, 2H), 6.73 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.53, 24.15, 39.72, 40.71, 60.76, 107.33, 120.88, 148.61, 168.75; MS (ES^+): *m*/*z*=287.1 $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{15}H_{20}NaO_4$ $[M-Na^+]$ 287.1254, found 287.1250.

4.10. Ethyl-spiro(benzo[1,3]dioxole-2,1′-cycloheptane)-2′-carboxylate (9)

Upon distillation of the crude product (127 °C, 2.3×10^{-2} mbar), the ketal (9.6 g, 35%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.86 (t, *J*=7.10 Hz, 3H), 1.42–1.71 (m, 5H), 1.78–1.98 (m, 3H), 2.04–2.20 (m, 2H), 3.06 (dd, *J*=3.30 Hz, 1H), 3.88 (q, *J*=9.30 Hz, 2H), 6.64–6.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.60, 21.22, 25.35, 26.75, 28.00, 38.27, 54.00, 60.56, 108.17, 108.26, 120.00, 120.97, 121.01, 146.92, 147.43, 171.57; MS (EI): *m*/*z* (%)=276.1 (44) $[M]^{\bullet+}$. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.64; H, 7.32.

4.11. Ethyl-2′-methyl-spiro(benzo[1,3]dioxole-2,1′-cycloheptane)-2′-carboxylate (10)

Upon distillation of the crude product (132 °C, 2.1×10^{-2} mbar), the ketal (4.3 g, 70%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (t, *J*=7.1 Hz, 3H), 1.33 (s, 3H), 1.57–1.82 (m, 7H), 2.07–2.17 (m, 2H), 2.40–2.46 (m, 1H), 4.09 (q, *J*=7.1 Hz, 2H), 6.75 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.84, 20.52, 20.85, 23.05, 26.78, 33.85, 35.87, 54.81, 60.60, 107.99, 108.27, 120.85, 120.86, 121.29, 147.22, 147.71, 174.02; MS (EI): *m*/*z* (%)=290.1 (20) $[M]^{\bullet+}$. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.27; H, 7.63.

4.12. Ethyl-2′-methyl-spiro(benzo[1,3]dioxole-2,1′-cyclohexane)-2′-carboxylate (11)

Upon distillation of the crude product (131 °C, 3.2×10^{-2} mbar), the ketal (6.4 g, 72%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.08 (t, J=7.1 Hz, 3H), 1.33 (s, 3H), 1.45–1.61 (m, 2H), 1.67–1.81 (m, 3H), 1.93–1.99 (m, 1H), 2.13 (ddd, J=13.6, 7.3, 4.0 Hz, 1H), 2.23 (ddd, J=13.8, 7.0, 3.9 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 6.73–6.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.84, 18.37, 21.26, 22.64, 32.47, 34.04, 51.09, 60.59, 107.94, 108.31, 119.04, 120.81, 120.91, 147.41, 147.43, 173.72; MS (EI): m/z (%)=276.1 (44) $[M]^{\bullet+}$; HRMS: m/z calcd for $C_{16}H_{20}NaO_4$ $[M+Na]^+$ 299.1254, found 299.1251.

4.13. 2-(1,1-Dimethylethyl)-2-(2-hydroxyethyl)-benzo[1,3]dioxole (12)

To an ice cooled solution of **8** (0.264 g, 1 mmol) in diethyl ether (20 mL) was added $LiAlH_4$ (0.16 g, 4 mmol). The reaction mixture was stirred for 3 h at reflux and then carefully poured onto ice water. The organic phase was separated and the aqueous phase was extracted with *t*-BuOMe (100 mL). The organic layer was washed several times with H_2O (5×50 mL) and brine (50 mL), dried (anhyd $MgSO_4$), filtered, and evaporated to give **12** (0.17 g, 77%) as a colorless powder. Mp 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.04 (s, 9H), 1.81 (s, 1H), 2.27 (t, J=6.12 Hz, 2H), 3.75 (t, J=6.12 Hz, 2H), 6.73–6.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.23, 36.45, 40.44, 57.82, 107.34, 121.05, 123.77, 148.51; MS (EI, 70 eV): m/z (%)=222.1 (19) $[M]^{\bullet+}$. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.25; H, 8.26.

4.14. 2-(2-Acetoxyethyl)-2-(1,1-dimethylethyl)-benzo[1,3]dioxole (13)

To a solution of **12** (0.11 g, 0.5 mmol) in pyridine (5 mL), 1 mL of acetic acid anhydride was added. The reaction mixture was stirred overnight at rt, poured onto ice water and extracted with *t*-BuOMe (100 mL). The organic layer was washed several times with H_2O (5×50 mL) and brine (50 mL), dried (anhyd $MgSO_4$), filtered, and evaporated to give **13** (0.11 g, 86%) as a colorless powder. Mp 36–37 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.04 (s, 9H), 1.90 (s, 3H), 2.32 (t, J=7.1 Hz, 2H), 4.17 (t, J=7.1 Hz, 2H), 6.70–6.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.24, 32.82, 40.48, 59.61, 107.34, 121.93, 122.18, 148.52, 170.88; MS (EI, 70 eV): m/z (%)=264.1 (13) $[M]^{\bullet+}$. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.76; H, 7.63. Found: C, 68.54; H, 7.737.

4.15. 2-(1,1-Dimethylethyl)-2-(2-isobutyryloxyethyl)-benzo[1,3]dioxole (14)

To a solution of **12** (0.55 g, 2.5 mmol) in pyridine (20 mL), 3 mL of isobutyric acid anhydride was added. The reaction mixture was stirred overnight at rt, poured onto ice water and extracted with *t*-BuOMe (150 mL). The organic layer was washed with H_2O (5×50 mL) and brine (50 mL), dried (anhyd $MgSO_4$), filtered, and evaporated to furnish **14** (0.58 g, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.04 (s, 9H), 1.09 (d, J=7.0 Hz, 6H), 2.31 (t, J=7.0 Hz, 2H), 2.37–2.42 (m, 1H), 4.17 (t, J=7.0 Hz, 2H), 6.70–6.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.21, 30.89, 32.88, 33.84, 40.43, 59.36, 107.29, 120.86, 122.20, 148.48, 176.95; MS (EI, 70 eV): m/z (%)=292.1 (10) $[M]^{\bullet+}$; HRMS: m/z calcd for $C_{17}H_{24}O_4$ $[M]^+$ 292.1675, found 292.1675.

4.16. 2-(1,1-Dimethylethyl)-2-(2-(4-methylphenyl-sulfonyloxy)-ethyl)benzo[1,3]dioxole (15)

A solution of **12** (0.11 g, 0.5 mmol) in pyridine (5 mL) was treated with 4-toluenesulfonyl chloride (0.15 g, 0.75 mmol). The reaction mixture was stirred overnight at rt. Then poured onto ice water. The formed solid was filtered off, washed with pure water (3×50 mL) to give tosylate **15** (0.14 g, 80%) as a colorless powder. Mp 46–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.97 (s, 9H), 2.35 (t, J=7.3 Hz, 2H), 2.41 (s, 3H), 4.11 (t, J=7.3 Hz, 2H), 6.62–6.64 (m, 2H), 6.71–6.73 (m, 2H), 7.24 (d, J=8.0 Hz, 2H), 7.61 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.59, 24.09, 33.42, 40.37, 65.44, 107.44, 121.07, 121.62, 127.78, 129.72, 132.84, 144.59, 148.12; MS (EI, 70 eV): m/z (%)=376.1 (14) $[M]^{\bullet+}$. Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43; S, 8.52. Found: C, 63.84; H, 6.52; S, 8.79.

4.17. 2-(1,1-Dimethylethyl)-2-(2-cyanoethyl)-benzo[1,3]dioxole (16)

A mixture of tosylate **15** (0.1 g, 0.27 mmol) and sodium cyanide (0.02 g, 0.4 mmol) in dimethylsulfoxide (5 mL) was stirred at 80 °C for 2 h. Then poured onto ice water. The formed solid was filtered off, washed with pure water (3×50 mL) to give **16** (0.051 g, 84%) as a colorless powder. Mp 44–45 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.04 (s, 9H), 2.35–2.37 (m, 2H), 2.38–2.40 (m, 2H), 6.73–6.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=10.92, 24.24, 30.32, 40.33, 107.48, 119.36, 121.32, 121.62, 148.34; MS (EI, 70 eV): m/z (%)=231.1 (16) $[M]^{\bullet+}$. Anal. Calcd for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.21; H, 7.37; N, 5.97.

4.18. 2-(3,3-Dicyanopropyl)-2-(1,1-dimethylethyl)-benzo[1,3]dioxole (17)

A mixture of malononitrile (1.75 g, 27 mmol) and K_2CO_3 (3.7 g, 27 mmol) in DMF (30 mL) was stirred for about 30 min at rt. Then, tosylate **15** (2 g, 6 mmol) was added. The reaction mixture was stirred for 3 h at 80 °C, poured onto ice water and was extracted with ethylacetate (200 mL). The organic layer was washed with H_2O (3×100 mL) and brine (100 mL), dried (anhyd $MgSO_4$), and filtered. Removal of the solvent afforded a residue, which was chromatographed using cyclohexane–ethylacetate (9.5:0.5) as eluent to give **17** (0.60 g, 42%) as a colorless powder. Mp 56–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.05 (s, 9H), 2.10–2.16 (m, 2H), 2.25–2.29 (m, 2H), 3.77 (t, J=6.9 Hz, 1H), 6.73–6.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.50, 24.24, 24.38, 30.63, 40.49, 107.49, 112.27, 121.45, 122.29, 148.25; MS (EI, 70 eV): m/z (%)=270.1 (12) $[M]^{\bullet+}$; HRMS: m/z calcd for $C_{16}H_{18}N_2O_2$ $[M]^+$ 270.1368, found 270.1363.

4.19. 2-(1,1-Dimethylethyl)-2-(2-iodoethyl)benzo[1,3]-dioxole (18)

A mixture of the tosylate **15** (0.377 g, 1 mmol) and sodium iodide (0.6 g, 4 mmol) in acetone (20 mL) was refluxed under inert atmosphere for about 20 h. Then, the solvent was removed under reduced pressure. Water was added to the residue, which was extracted with ethylacetate (100 mL). The combined extracts were washed with H_2O (3×50 mL) and brine (50 mL), dried (anhyd $MgSO_4$), filtered, and evaporated to give iodide **18** (0.27 g, 81%) as yellow needles. Mp 67–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.04 (s, 9H), 2.55–2.61 (m, 2H), 3.08–3.13 (m, 2H), 6.70–6.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−4.50, 24.23, 39.84, 39.94, 107.24, 120.94, 123.19, 148.52; MS (EI, 70 eV): m/z (%)=332.0 (18) $[M]^{\bullet+}$. Anal. Calcd for $C_{13}H_{17}IO_2$: C, 47.00; H, 5.16. Found: C, 46.95; H, 5.26.

4.20. 2-(1,1-Dimethylethyl)-2-(2-nitroethyl)-benzo[1,3]dioxole (19)

A mixture of the iodide **18** (2 g, 6 mmol) and sodium nitrite (1.25 g, 18 mmol) in DMF (20 mL) was kept at ambient conditions for 5 h. The mixture was poured onto ice water. It was extracted

with *t*-BuOMe (300 mL), and the combined extracts were washed with H_2O (3×200 mL) and brine (200 mL), dried (anhyd $MgSO_4$), and filtered. Removal of the solvent afforded a residue, which was chromatographed using cyclohexane–ethylacetate (9.5:0.5) as eluent to give **19** (0.72 g, 48%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.06 (s, 9H), 2.75 (t, J=8.0 Hz, 2H), 4.42 (t, J=8.0 Hz, 2H), 6.72–6.75 (m, 2H), 6.77–6.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.21, 31.98, 40.41, 69.94, 107.60, 121.49, 148.14; MS (EI, 70 eV): m/z (%)=251.2 (14) $[M]^{\bullet+}$; HRMS: m/z calcd for $C_{13}H_{17}NO_4$ $[M]^+$ 251.1158, found 251.1159.

4.21. 2-(Carboxylmethyl)-2-(1,1-dimethylethyl)-benzo[1,3]dioxole (20)

A solution of **8** (2.15 g, 8 mmol) in THF and H_2O (3:1, 70 mL) was treated with lithium hydroxide (0.6 g, 24 mmol) and stirred for 4 days at room temperature. The mixture was diluted with H_2O, acidified with 1 M hydrochloric acid (30 mL), and immediately extracted with ethylacetate (100 mL). The organic layer was washed several times with H_2O (3×50 mL) and brine (50 mL), dried (anhyd $MgSO_4$), and filtered. Removal of the solvent gave acid **20** (1.40 g, 73%) as colorless needles. Mp 132–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.06 (s, 9H), 2.95 (s, 2H), 6.69–6.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.19, 39.01, 40.86, 107.56, 120.22, 121.10, 148.31, 174.16; MS (ES^+): m/z=259.1 $[M+Na]^+$; HRMS: m/z calcd for $C_{13}H_{16}NaO_4$ $[M-Na^+]$ 259.0941, found 259.0950.

4.22. 2-(Carboxamidoylmethyl)-2-(1,1-dimethylethyl)-benzo[1,3]dioxole (21)

A solution of acid **20** (0.4 g, 1.7 mmol) in CH_2Cl_2 (10 mL) at room temperature was treated with *N*,*N*′-dicyclohexyl carbodiimide (0.35 g, 1.7 mmol) and the mixture was stirred for 1 h. 4-*N*,*N*-Dimethylaminopyridine (0.02 g, 0.17 mmol) was added and the stirring was continued for an additional 1 h. The reaction mixture was treated with aqueous ammonia (3 mL). After being stirred overnight, the mixture was filtered, then CH_2Cl_2 (50 mL) was added to the filtrate. The organic layer was washed with H_2O (3×50 mL), Na_2CO_3 solution (50 mL), and brine (50 mL), dried (anhyd $MgSO_4$), and filtered. Removal of the solvent afforded a residue, which was crystallized using cyclohexane to give **21** (0.27 g, 68%) as colorless needles. Mp 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.07 (s, 9H), 2.89 (s, 2H), 5.97 (br, 2H), 6.73–6.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.36, 40.92, 41.13, 107.92, 121.11, 121.41, 148.00, 170.39; MS (EI, 70 eV): m/z (%)=235.1 (28) $[M]^{\bullet+}$. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.45; H, 7.35; N, 6.06.

4.23. 2-(Cyanomethyl)-2-(1,1-dimethylethyl)-benzo[1,3]dioxole (22)

To a solution of the amide **21** (0.117 g, 0.5 mmol) in pyridine (10 mL), 4-toluenesulfonyl chloride (0.2 g, 1 mmol) is added. The reaction mixture was stirred overnight at rt, poured onto ice water. The solid was filtered off, washed by water (50 mL) to give nitrile **22** (0.96 g, 88%) as colorless powder. Mp 91–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 9H), 2.98 (s, 2H), 6.8–6.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.00, 24.29, 40.09, 108.23, 115.28, 118.55, 121.80, 147.50; MS (EI, 70 eV): m/z (%)=217.1 (24) $[M]^{\bullet+}$; HRMS: m/z calcd for $C_{13}H_{15}NO_2$ $[M]^+$ 217.1103, found 217.1102.

4.24. 2-(Butoxycarbonylmethyl)-2-(1,1-dimethylethyl)-benzo[1,3]dioxole (23)

To an ice cooled solution of **20** (3.5 g, 15 mmol) in dry DMF (75 mL), NaH (0.62 g, 60%, 15 mmol) was added. The reaction mixture is stirred until evolution of gas ceased. Then, *n*-butyliodide (2.8 g, 15 mmol) was added. Upon warming to ambient temperature the mixture is stirred for 14 h. The reaction mixture was fractionated was with *t*-BuOMe (150 mL) and 1 M hydrochloric acid (100 mL). The organic layer was washed with H_2O (5×100 mL) and brine (100 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed using cyclohexane–ethylacetate (9:1) as eluent to give **23** (3.7 g, 86%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.82 (t, J=6.5 Hz, 3H), 1.06 (s, 9H), 1.13–1.32 (m, 4H), 2.97 (s, 2H), 3.83 (t, J=7.1 Hz, 2H), 6.69–6.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.61, 18.94, 24.17, 30.16, 39.64, 40.76, 64.74, 107.35, 120.60, 120.87, 148.59, 168.89; MS (EI): m/z (%)=292.2 (15) $[M]^{\bullet+}$. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27; Found: C, 69.81; H, 8.03.

4.25. 2-(1,1-Dimethylethyl)-2-(2-methoxyethoxy-carbonylmethyl)benzo[1,3]dioxole (24)

To an ice cooled solution of **20** (2.3 g, 10 mmol) in dry CH_2Cl_2 (100 mL), *N*,*N*′-dicyclohexyl carbodiimide (2.2 g, 10 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.13 g, 1 mmol) were added. The reaction mixture was stirred for about 10 min and after that, 2-methoxyethanol (0.9 g, 12 mmol) was added. On warming up on ambient temperature the mixture is stirred for 14 h. The colorless precipitate formed during the reaction is removed by filtration and subsequently washed with (25 mL) cold CH_2Cl_2. The filtrate was concentrated under reduced pressure. The residue was chromatographed using cyclohexane–ethylacetate (8:2) as eluent to give **23** (2.4 g, 84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.05 (s, 9H), 3.01 (s, 2H), 3.23 (dd, J=4.4 Hz, 2H), 3.27 (s, 3H), 3.96 (dd, J=5.4 Hz, 2H), 6.69–6.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.11, 39.31, 40.69, 58.73, 63.60, 69.82, 107.29, 120.52, 120.84, 148.60, 168.65; MS (EI): m/z (%)=294.1 (20) $[M]^{\bullet+}$; Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53; Found: C, 65.50; H, 7.55.

4.26. 2-(1,1-Dimethylethyl)-2-((methyloxycarbonylmethyl)-oxycarbonylmethyl)benzo[1,3]dioxole (25)

To an ice cooled solution of **20** (4.3 g, 18 mmol) in dry DMF (75 mL) was added NaH (0.76 g, 60%, 19 mmol). The reaction mixture is stirred until evolution of gas ceased, bromoacetatemethyl ester (2.9 g, 19 mmol) and NaI (0.3 g, 2 mmol) were added. Upon warming to ambient temperature the mixture is stirred for 16 h. The reaction mixture was fractionated was with *t*-BuOMe (200 mL) and 1 M hydrochloric acid (100 mL). The organic layer was washed with H_2O (5×100 mL) and brine (100 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed using cyclohexane–ethylacetate (8:2) as eluent to give **25** (5.0 g, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.07 (s, 9H), 3.09 (s, 2H), 3.68 (s, 3H), 4.36 (s, 2H), 6.70–6.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.17, 38.74, 40.72, 52.12, 60.73, 107.41, 120.35, 120.98, 148.46, 167.83, 167.95; MS (EI): m/z (%)=308.2 (12) $[M]^{\bullet+}$. Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54; Found: C, 61.97; H, 6.76.

4.27. 2-(2-Chloroethoxycarbonylmethyl)-2-(1,1-dimethyl-ethyl)benzo[1,3]dioxole (26)

To an ice cooled solution of **20** (4.5 g, 19 mmol) in dry DMF (100 mL) was added NaH (0.77 g, 60%, 19 mmol). The reaction mixture is stirred until evolution of gas ceased, 1,2-dichloroethane (18.8 g, 190 mmol) was added. Upon warming to ambient temperature the mixture is stirred for 16 h. The reaction mixture was fractionated with *t*-BuOMe (200 mL) and 1 M hydrochloric acid (100 mL). The organic layer was washed with H_2O (5×100 mL) and brine (100 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed using

cyclohexane–ethylacetate (9:1) as eluent to give **26** (3.4 g, 59%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.07 (s, 9H), 3.02 (s, 2H), 3.22 (t, J=6.1 Hz, 2H), 4.06 (t, J=6.1 Hz, 2H), 6.72–6.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.13, 39.40, 40.62, 40.73, 64.19, 107.43, 120.52, 121.03, 148.52, 168.40; MS (EI): MS (EI): m/z (%)=298.2 (16) $[M]^{\bullet+}$; HRMS: m/z calcd for $C_{15}H_{19}ClNaO_4$ $[M-Na^+]$ 321.0864, found 321.0867.

4.28. 2-(1,1-Dimethylethyl)-2-(*N*-morpholinocarbonylmethyl)benzo[1,3]dioxole (27)

In a 25 mL one-necked flask, **8** (2.5 g, 10 mmol) was dissolved in 10 mL morpholine. The mixture was heated to reflux for about 48 h. After concentration under reduced pressure, the resulting oil was fractionated with *t*-BuOMe (150 mL) and 1 M hydrochloric acid (30 mL). The organic layer was washed with H_2O (5×100 mL) and brine (100 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed using cyclohexane–ethylacetate (1:1) as eluent to give **27** (2.1 g, 70%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.09 (s, 9H), 3.04 (s, 2H), 3.36–3.42 (m, 4H), 3.48–3.63 (m, 4H), 6.73–6.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.19, 37.41, 40.73, 41.89, 47.29, 66.35, 66.55, 107.54, 121.11, 121.54, 148.00, 166.48; MS (EI): m/z (%)=305.2 (22) $[M]^{\bullet+}$; HRMS: m/z calcd for $C_{17}H_{23}NNaO_4$ $[M-H^+]$ 328.1519, found 328.1513.

4.29. 2-(2-*N*,*N*-Diethylcarboxamidomethyl)-2-(1,1-dimethylethyl)benzo[1,3]dioxole (28)

To an ice cooled solution of **20** (3.4 g, 14 mmol) in dry CH_2Cl_2 (100 mL), *N*,*N*′-dicyclohexyl carbodiimide (3.0 g, 14 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.173 g, 1.4 mmol) were added. The reaction mixture was stirred for about 10 min and after that, diethylamine (2.0 g, 28 mmol) was added. Upon warming to ambient temperature the mixture is stirred for 14 h. The colorless precipitate formed during the reaction is removed by filtration and washed with (25 mL) cold CH_2Cl_2. The solvent was concentrated under reduced pressure. The residue was chromatographed using cyclohexane–ethylacetate (1:1) as eluent to give **28** (2.35 g, 55%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.58 (t, J=7.0 Hz, 3H), 1.09 (s, 9H), 1.12 (t, J=7.0 Hz, 3H), 3.15 (q, J=7.0 Hz, 2H), 3.39 (q, J=7.0 Hz, 2H), 6.73–6.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.80, 13.78, 24.23, 37.49, 39.71, 40.51, 42.19, 107.42, 120.89, 121.53, 148.16, 166.97; MS (EI): m/z (%)=291.2 (18) $[M]^{\bullet+}$; HRMS: m/z calcd for $C_{17}H_{26}NO_3$ $[M+H^+]$ 292.1907, found 292.1899.

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References and notes

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