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Alkaloid Synthesis

# Total Synthesis of (±)-Scopolamine: Challenges of the Tropane Ring

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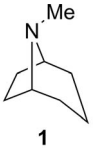
*Dedicated to Professor Dr. Dr. h.c. mult. Wittko Francke on the occasion of his 75th birthday*

**Abstract:** Scopolamine was synthesized using 6,7-dehydrotropine as a key intermediate. Rhodium-catalyzed [4 + 3] cycloaddition chemistry and a modified Robinson–Schöpf reaction were each independently evaluated for their utility in constructing the tropane core. Both synthetic approaches gave comparable overall yields.

## Introduction

Tropane alkaloids are among the oldest medicines known to mankind and possess a wide range a biological activities.[1–4] This family is comprised of roughly 200 alkaloids with the name tropane which designates the *N*-methyl-8-azabicyclo[3.2.1]-octane framework (**1**) (Figure 1) as a key structural component. These alkaloids started to be isolated from plants around 1830 and are mainly found in the *Solanaceae* family but also are known in the *Convolvulaceae*, *Erythroxylaceae*, *Proteaceae*, and *Rhizophoraceae* families.[1,4,5]




**1**

*N*-Methyl-8-azabicyclo[3.2.1]octane

Figure 1. The tropane ring system.

The economically important tropane alkaloids are predominantly obtained by extraction from plants. Among them, scopolamine (**2**), also known as hyoscine, is highly valuable due to its widespread medical applications ranging from induction of antiemetic effects and inhibition of motion sickness to resuscitation.[3,5] *Datura* is among the most alkaloid-rich natural plant genera but usually contains only 0.2–0.8 % of total alkaloids. The concentration of scopolamine in these species is rather low.[3] Only one total synthesis of scopolamine has been described so far,[6] even though precursors to the final product have been reported,[7] as in the syntheses of related alkaloids such as anisodine (**3**),[8,9] or scopine.[10] In the course of our work on the synthesis of alkaloids, we became interested in a synthetic approach to scopolamine. We reasoned that 6,7-dehydrotropine (**4**) could serve as a key, and potentially broadly applicable, intermediate since the oxirane ring is likely to cause side reactions when present at an early stage of the synthesis. Compound **4** could be used as a common precursor for several alkaloids such as scopolamine (**2**), anisodine (**3**),[8] hyoscyamine (**5**), or anisodamine (**6**) (Figure 2). Herein, we describe the total synthesis of scopolamine (**2**) from key intermediate **4**.

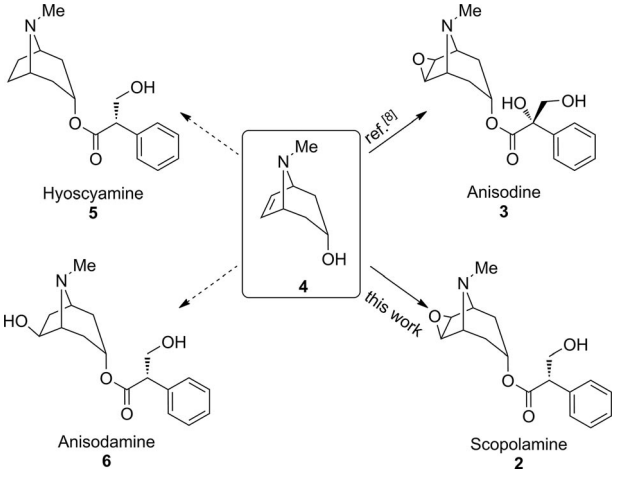



Figure 2. 6,7-Dehydrotropine (**4**) as a synthetic precursor to assorted tropanes.

## Results and Discussion

Our first retrosynthetic approach to 6,7-dehydrotropine (**4**) called for dealkoxycarbonylation of keto ester **7**. The tropane skeleton could be formed in a [4 + 3] cycloaddition between pyrrole **8** and diazo ester **9** as the key step (Figure 3). Even though [4 + 3] cycloadditions involving oxyallyl cations are well known with furans and cyclopentadienes, examples of their use with pyrroles are limited.[11–13] However, Davies et al. reported

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in 1997 the synthesis of tropanes by a rhodium-catalyzed [4 + 3] cycloaddition between a chiral vinyl diazoacetate and *N*-Boc-pyrrole.[14] This reaction was later exploited during the asymmetric synthesis of tropanes by the same group as well as by Riché and co-workers.[15,16] Even though this process might not be scalable, it held promise as an easy and quick route to key intermediate **4**.

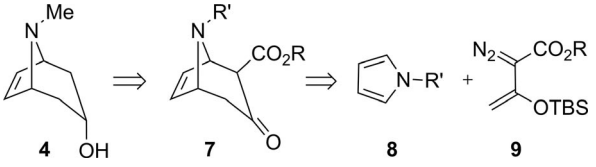
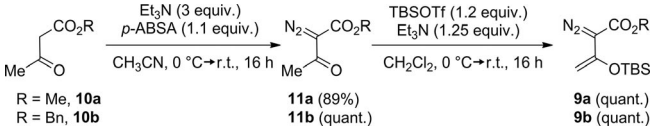



Figure 3. Retrosynthetic analysis of **4** calling for [4 + 3] cycloaddition.

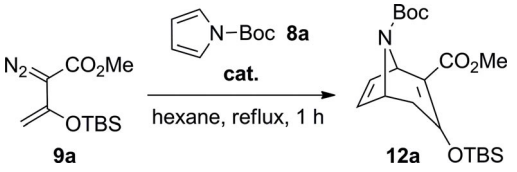
Diazo esters **11** were obtained from acetoacetates **10** in 89 % to quantitative yield using 4-acetamidobenzenesulfonyl azide (*p*-ABSA) as a safe diazo transfer agent (Scheme 1).[17,18] TBS enol ethers **9** were obtained in quantitative yield from esters **11**.




Scheme 1. Formation of diazo acetates **9**.

Application of Davies' conditions to methyl ester **9a** furnished the desired product **12a** in 53 % yield (Table 1, Entry 1). When CuI was used as a catalyst instead of $Rh_2(OOct)_4$, no reaction occurred (Table 1, Entry 2). Using $CH_2Cl_2$ instead of hexane was also detrimental to the reaction (Table 1, Entry 3). Decreasing the amount of pyrrole **8a** to 2.5 equiv. did not diminish the yield and up to 60 % of desired product **12a** was isolated (Table 1, Entries 4 and 5). However, a further reduction in the amount of pyrrole **8a** led to a drop in yield of **12a** (Table 1, Entry 6).

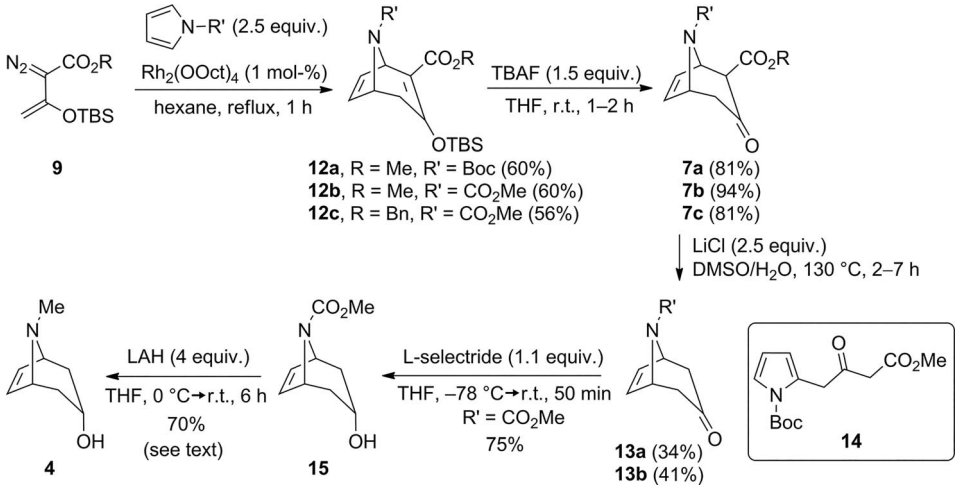
Table 1. [4 + 3] cycloaddition optimization between **8a** and **9a**.[a]




| Entry | **8a** [equiv.] | Catalyst. | Yield [%] |
|---|---|---|---|
| 1 | 5 | $Rh_2(OOct)_4$ (1 mol-%) | 53 |
| 2 | 5 | CuI (5 mol-%) | – |
| 3[b] | 5 | $Rh_2(OOct)_4$ (1 mol-%) | 33 |
| 4 | 2.5 | $Rh_2(OOct)_4$ (1 mol-%) | 53 |
| 5[c] | 2.5 | $Rh_2(OOct)_4$ (1 mol-%) | 60 |
| 6 | 1.2 | $Rh_2(OOct)_4$ (1 mol-%) | 48 |

[a] Reaction performed on a 0.39 mmol scale. [b] Reaction performed in refluxing $CH_2Cl_2$ (6 h). [c] Reaction performed on a 1.55 mmol scale.

Removal of the silyl group using TBAF led to desired keto esters **7** in 81–94 % yield (Scheme 2). Next, the dealkoxycarbonylation of **7** was investigated. After a short screening of Krapcho-type conditions,[19] desired ketone **13a** was obtained from **7a** in a maximum yield of 34 % using LiCl in DMSO. Formation of pyrrole **14** resulting from a retro-Mannich reaction was also observed.[20] Since the moderate yield may have been the result of the known sensitivity of the *N*-Boc group to high temperatures, *N*-methoxycarbonyl derivative **7b** was synthesized from **9a** in 56 % over two steps. In this case, dealkoxycarbonylation product **13b** was obtained in 41 % yield. This result showed that the *N*-Boc protecting group was only partially responsible for the low yield of **13**. Alternative methods for dealkoxycarbonylation were also investigated. Using basic aluminum oxide, **13b** was isolated in 36 % yield from **7b**. Compound **7c**, bearing a benzyl ester moiety, was then synthesized. We envisioned that facile *O*-debenzylation would lead to the corresponding α-keto carboxylic acid which should spontaneously decarboxylate to give **13b**. However, the use of $BCl_3$,[21] Raney nickel,[22] $Na_2S$,[23] TMSCl/NaI[24] and $PdCl_2/Et_3SiH$[25] all failed to give desired decarboxylated product. Hydrogenolysis as a




Scheme 2. Generation of alcohol **4** from keto ester **7**.

means of *O*-debenzylation was not attempted since retention of the 6,7-double bond was essential.

With desired tropinone **13b** in hand, diastereoselective ketone reduction with L-selectride® yielded the desired *N*-methoxycarbonyl-6,7-dehydrotropinone **15** in 75 % yield. The carbamate moiety was then reduced to the *N*-methyl group with LAH thus rendering **4** in 70 % yield as a mixture with the triethylamine-derived salt ($Et_3N^+CH_2Cl\ Cl^-$). This salt was formed from the eluent ($CH_2Cl_2$/MeOH, 3:97 + 10 % $Et_3N$) used in the chromatographic purification step.[26–28] The *N*-methyl group in **4** could alternatively be introduced by dealkoxycarbonylation with TMSI followed by reductive methylation.[29]

Due to the moderate yields encountered for dealkoxycarbonylation of **7**, the use of potentially hazardous diazo compounds **9** and the expensive catalyst [$Rh_2(OOct)_4$], an alternative pathway was investigated. Another attractive method for the construction of the tropinone skeleton was realized by Robinson in 1917 (later optimized by Schöpf) who used an ingenious three component one-pot reaction between succinaldehyde, methylamine hydrochloride and acetonedicarboxylic acid.[30,31] Our second retrosynthetic approach to **4** involved the elimination of the hydroxy group in 6-hydroxytropinone (**16**) to generate the 6,7-double bond (Figure 4). Alcohol **16** would be obtained by a modified Robinson–Schöpf reaction using hydroxysuccinaldehyde (**17**).[32,33]

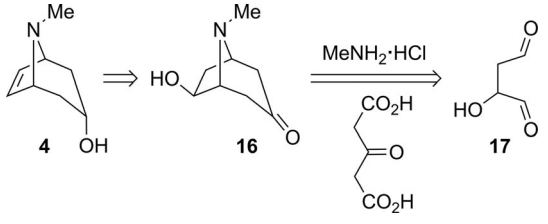
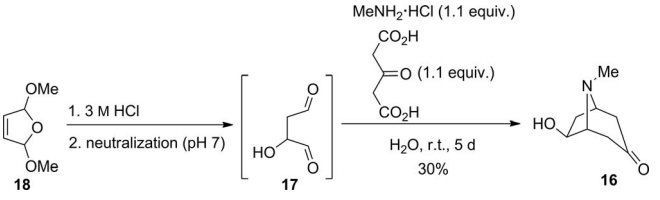


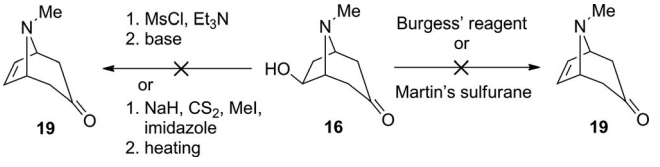

Figure 4. Retrosynthetic analysis calling for a modified Robinson synthesis.

Thus, a modified Robinson reaction using commercial 2,5-dimethoxy-2,5-dihydrofuran (**18**) as the hydroxysuccinaldehyde precursor was carried out to form 6-hydroxytropinone (**16**) in 30 % yield (Scheme 3). Even though the yield of **16** is moderate, the reaction is performed in water at ambient temperature and only involves inexpensive starting materials. Use of the corresponding diester instead of acetonedicarboxylic acid and subsequent hydrolysis/decarboxylation gave a slightly lower overall yield (data not shown).




Scheme 3. Modified Robinson–Schöpf reaction using hydroxysuccinaldehyde **17**.

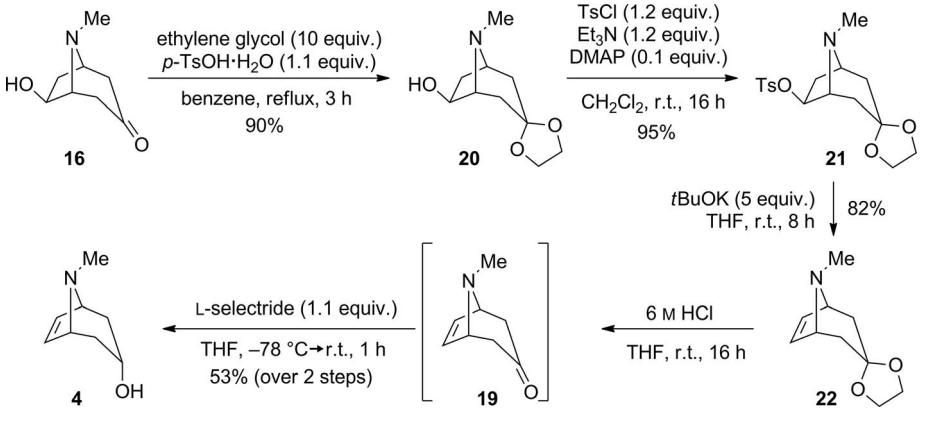
Mesylation of alcohol **16** followed by elimination using a base (DBU, *t*BuOK) led only to decomposition (Scheme 4). Thermal elimination of the *S*-methyl xanthate derivative of **16** also failed to render **19**. Attempts at direct elimination of **16** using Burgess' reagent or Martin's sulfurane only led to decomposition.



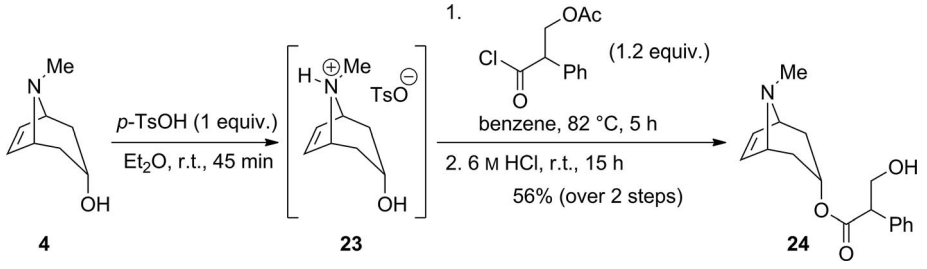

Scheme 4. Elimination attempts with alcohol **16**.

Assuming that the encountered difficulties with elimination were due to the presence of the free keto group, **16** was converted to ethylene glycol ketal **20** in 90 % yield (Scheme 5).[34] Even though benzene as the solvent for keto protection gave the best yields of **20**, the less toxic solvents toluene or acetonitrile gave comparable results. Tosylation of alcohol **20** gave sulfonate **21** which produced the desired olefin **22** in 82 % yield upon subjection to *t*BuOK and subsequent elimination. Deprotection of the acetal followed by reduction with L-selectride® afforded 6,7-dehydrotropine **4** in 53 % yield over two steps.

Introduction of the tropic acid part was carried out by esterification between acetyltropic acid chloride and alcohol **23** using Čeković's procedure;[7] desired ester **24** was generated in 56 % yield over the two steps as a mixture with alcohol **4** (10 % yield) which was removed in the subsequent step (Scheme 6). The use of ammonium salt **23** in the *O*-acylation proved crucial



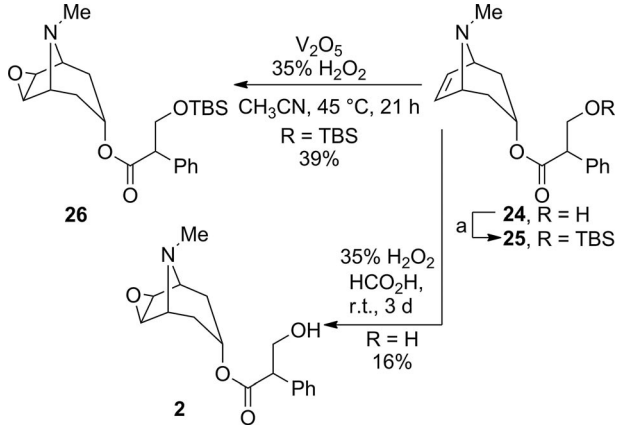

Scheme 5. Elimination of the hydroxy moiety.




Scheme 6. Esterification of tropine **4**.

for the esterification process since only acetylation of the hydroxy group occurred when alcohol **4** was used as the substrate without prior protonation.

Desired scopolamine **2** was then obtained by $H_2O_2$-mediated epoxidation of alkene **24** in only 16 % yield (Scheme 7). The application of other epoxidation conditions ($V_2O_5/H_2O_2$ or *m*-CPBA) led only to partial recovery of starting material. This low yield of **2** may be due, in part, to concomitant formation of *N*-oxide of **2**. Interestingly, when the primary alcohol was TBS protected, epoxidation of **25** rendered the desired product **26** in 39 % yield. However, attempts to remove the TBS group led to decomposition of starting material **26**. It should be noted, however, that the final step yields *en route* to **26** were not optimized and that higher yields have been reported for similar substrates.




Scheme 7. Epoxidation of alkenes **24** and **25**; a: TBSCl (1.2 equiv.), imidazole (1.7 equiv.), $CH_2Cl_2$, r.t., 16 h, 68 %.

## Conclusions

In summary, scopolamine (**2**) has been synthesized in nine linear steps including a modified Robinson–Schöpf reaction from cheap starting materials. An approach via [4 + 3] cycloaddition to form the tropane ring proved to be problematic due to a low-yielding dealkoxycarboxylation of intermediate α-keto esters and resulted in a slightly lower overall yield. Elimination of 6-hydroxytropine was found to be feasible only if the keto group was protected. In terms of chemical yields, chemoselective epoxidation of the 6,7-double bond proved to be the single greatest limitation to this approach; no optimization of the presented endgame has, however, been undertaken thus far.

## Experimental Section

**Materials and Methods:** All commercially available reagents were reagent grade and used without further purification. Reactions involving moisture or air sensitive reagents were performed under an argon atmosphere in oven-dried glassware. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Dichloromethane ($CH_2Cl_2$), hexane and benzene were distilled from calcium hydride. Triethylamine ($Et_3N$) was distilled from KOH and stored over KOH under an argon atmosphere. Thin layer chromatography (TLC) was carried out on 0.25 mm silica gel plates (60 $F_{254}$) using UV light as a visualizing agent and colorized with a Seebach reagent or potassium permanganate and heat as a developing agent. Flash chromatography was performed using silica gel (35–70 μm) and the indicated solvent system. Melting points were determined using open capillary tubes. NMR spectra were recorded with a 300 MHz spectrometer (300 MHz $^1H$ and 75.5 MHz $^{13}C$), a 400 MHz spectrometer (400 MHz $^1H$ and 100.6 MHz $^{13}C$) and a 600 MHz spectrometer (600 MHz $^1H$, 150.9 MHz $^{13}C$). The chemical shifts were referenced to the deuterated solvent (e.g., for $CDCl_3$, $\delta$ = 7.26 ppm and 77.16 ppm for $^1H$ and $^{13}C$ NMR, respectively) and reported in parts per million (ppm, $\delta$) relative to tetramethylsilane (TMS, $\delta$ = 0.00 ppm).[35] Infrared spectra were recorded as FT-IR spectra using a diamond ATR unit. High-resolution masses were recorded using a Q-TOF-Instrument with a dual source and a suitable external calibrant.

**Methyl 2-Diazo-3-oxobutanoate (11a):** $Et_3N$ (0.90 mL, 6.46 mmol, 3 equiv.) was added dropwise to a solution of methyl acetoacetate (0.25 mL, 2.15 mmol, 1 equiv.) and *p*-ABSA (569 mg, 2.37 mmol, 1.1 equiv.) in $CH_3CN$ (11 mL) at 0 °C. The solution was warmed up to room temp. overnight. The mixture was placed in a freezer for 3 h, then filtered, washed with $Et_2O$/pentane (1:4, 4.1 mL) and concentrated under reduced pressure. $Et_2O$/pentane (1:2, 2.5 mL) was then added and the mixture was placed in a freezer for 3 h. The mixture was then filtered through a pad of Florisil/Celite (1:1, wt/wt, 414 mg) and washed with $Et_2O$/pentane (2:3, 8.3 mL). The filtrate was then concentrated under reduced pressure to give crude title compound (271 mg, 89 %) as a yellow oil which was used without further purification. $R_f$ = 0.51 (EtOAc/cyclohexane, 1:3). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 3.84 (s, 3 H, $OCH_3$), 2.48 (s, 3 H, $CH_3$) ppm. Spectroscopic data are in accordance with the literature.[17]

**Benzyl 2-Diazo-3-oxobutanoate (11b):** $Et_3N$ (1.1 mL, 7.54 mmol, 3 equiv.) was added dropwise to a solution of benzyl acetoacetate (0.45 mL, 2.51 mmol, 1 equiv.) and *p*-ABSA (655 mg,2.77 mmol, 1.1 equiv.) in $CH_3CN$ (12 mL) at 0 °C. The solution was stirred at 0 °C for 2 h, filtered, washed with $Et_2O$, concentrated under reduced pressure and diluted with $Et_2O$ (17 mL). The organic layer was washed with water (2 × 6.5 mL), then with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure to give the crude benzyl 2-diazo-3-oxobutanoate (581 mg, quant.) as a light yellow

solid which was used without further purification. $R_f$ = 0.61 (EtOAc/cyclohexane, 1:3). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.33 (m, 5 H, Ph), 5.27 (s, 2 H, $CH_2$Ph), 2.49 (s, 3 H, $CH_3$) ppm. Spectroscopic data are in accordance with the literature.[18]

**Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-2-diazobut-3-enoate (9a):** TBSOTf (0.53 mL, 2.29 mmol, 1.2 equiv.) was added to a solution of **11a** (271 mg, 1.91 mmol, 1 equiv.) and $Et_3N$ (0.33 mL, 2.38 mmol, 1.25 equiv.) in $CH_2Cl_2$ (5.5 mL) at 0 °C. The solution was stirred and warmed up to room temp. overnight. The solution was diluted in hexane (22 mL). The organic layer was washed with satd. aq. $NaHCO_3$ (2 × 14 mL), brine (14 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude silyl enol ether **9a** (516 mg, quant.) as an orange oil. $R_f$ = 0.62 (EtOAc/cyclohexane, 1:8). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.00 (d, $J$ = 2.1 Hz, 1 H, $CH_2$), 4.25 (d, $J$ = 2.1 Hz, 1 H, $CH_2$), 3.79 (s, 3 H, $OCH_3$), 0.91 [s, 9 H, $C(CH_3)_3$], 0.22 (s, 6 H, 2 $SiCH_3$) ppm. Spectroscopic data are in accordance with the literature.[17]

**Benzyl 3-[(*tert*-Butyldimethylsilyl)oxy]-2-diazobut-3-enoate (9b):** TBSOTf (1.0 mL, 4.45 mmol, 1.20 equiv.) was added to a solution of **11b** (810 mg, 3.71 mmol, 1 equiv.) and $Et_3N$ (0.65 mL, 4.64 mmol, 1.25 equiv.) in $CH_2Cl_2$ (11 mL) at 0 °C. The solution was stirred and warmed up to room temp. overnight and diluted in hexane (42 mL). It was washed with satd. aq. $NaHCO_3$ (2 × 26 mL), brine (26 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude silyl enol ether **9b** (1.23 g, quant.) as an orange oil. $R_f$ = 0.58 (EtOAc/cyclohexane, 1:3). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.43–7.30 (m, 5 H, Ph), 5.25 (s, 2 H, $CH_2$Ph), 5.02 (d, $J$ = 2.1 Hz, 1 H, $CH_2$), 4.26 (d, $J$ = 2.1 Hz, 1 H, $CH_2$), 0.92 [s, 9 H, $C(CH_3)_3$], 0.23 (s, 6 H, 2 $SiCH_3$) ppm. $^{13}$C NMR, HSQC, HMBC (75 MHz, $CDCl_3$): $\delta$ = 164.2 (COO), 140.8 ($Cq$ = $CH_2$), 136.0 (Cq-Ar), 128.7 (2 CH-Ar), 128.4 (CH-Ar), 128.2 (2 CH-Ar), 90.6 ($CH_2$), 66.4 ($CH_2$Ph), 25.7 [$C(CH_3)_3$], 18.2 [$C(CH_3)_3$], –4.7 (2 $SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 2101, 1709, 1069, 827, 783 cm$^{-1}$. HRMS (ESI) $m/z$ 333.1642 ([M + H]$^+$, calcd. for $C_{17}H_{25}N_2O_3Si$ 333.1634).

**8-*tert*-Butyl 2-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-8-azabicyclo[3.2.1]octa-2,6-diene-2,8-dicarboxylate (12a):** A solution of diazo compound **9a** (397 mg, 1.55 mmol, 1 equiv.) in hexane (32 mL) was added with a syringe pump (10 mL/h) to a refluxing solution of freshly distilled *N*-Boc-pyrrole (0.65 mL, 3.88 mmol, 2.5 equiv.) and $Rh_2(OOct)_4$ (12 mg, 15.5 µmol, 1 mol-%) in hexane (32 mL). After the end of the addition, reflux was maintained for 1 h. After cooling, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 1:1 to 1:12) to afford the desired cycloadduct **12a** (368 mg, 60 %) as a yellow oil. $R_f$ = 0.29 (EtOAc/cyclohexane, 1:6). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.51–6.47 (m, 1 H, 7-H), 5.91 (dd, $J$ = 5.9, 2.5 Hz, 1 H, 6-H), 5.21–5.07 (br. s, 1 H, 1-H or 5-H), 4.70–4.60 (br. s, 1 H, 1-H or 5-H), 3.72 (s, 3 H, $OCH_3$), 2.93–2.70 (m, 1 H, 4-$H_a$), 1.82 (d, $J$ = 17.9 Hz, 1 H, 4-$H_b$), 1.42 [s, 9 H, $C(CH_3)_3$], 0.93 [s, 9 H, $SiC(CH_3)_3$], 0.18 (s, 3 H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$) ppm. Spectroscopic data are in accordance with the literature.[16]

**2,8-Dimethyl 3-[(*tert*-Butyldimethylsilyl)oxy]-8-azabicyclo[3.2.1]-octa-2,6-diene-2,8-dicarboxylate (12b):** A solution of diazo compound **9a** (515 mg, 1.91 mmol, 1 equiv.) in hexane (39 mL) was added with a syringe pump (10 mL/h) to a refluxing solution of freshly distilled *N*-Moc-pyrrole (0.54 mL, 4.78 mmol, 2.5 equiv.) and $Rh_2(OOct)_4$ (15 mg, 19.1 µmol, 1 mol-%) in hexane (39 mL). After the end of the addition, reflux was maintained for 1 h. After cooling, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 1:7 to 1:5) to afford the desired cycloadduct **12b** (408 mg, 60 %) as a yellow oil. $R_f$ = 0.31 (EtOAc/cyclohexane, 1:4). $^1$H NMR, COSY (400 MHz, $CDCl_3$): $\delta$ = 6.55–6.44 (br. s, 1 H, H-7), 5.96–5.86 (br. s, 1 H, H-6), 5.31–5.14 (m, 1 H, H-1), 4.79–4.64 (m, 1 H, H-5), 3.72 (s, 3 H, $OCH_3$), 3.67 (s, 3 H, $OCH_3$), 2.92–2.65 (m, 1 H, H-4a), 1.85 (d, $J$ = 17.9 Hz, 1 H, H-4b), 0.92 [s, 9 H, $C(CH_3)_3$], 0.17 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$) ppm. $^{13}$C NMR, HSQC, HMBC (100 MHz): $\delta$ = 165.6 (CO), 158.4 (C-3), 154.2 (NCO), 138.4 (C-7), 127.6 (C-6), 115.2 (C-2), 56.5 (C-5), 56.3 (C-1), 52.7 ($OCH_3$), 51.2 ($OCH_3$), 33.1 (C-4), 25.8 [$C(CH_3)_3$], 18.5 [$C(CH_3)_3$], –3.60 ($SiCH_3$), –3.65 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 1707, 1686, 1603, 1198, 840, 779 cm$^{-1}$. HRMS (ESI) $m/z$ 376.1558 ([M + Na]$^+$, calcd. for $C_{17}H_{27}NO_5SiNa$ 376.1556).

**2-Benzyl 8-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-8-azabicyclo[3.2.1]octa-2,6-diene-2,8-dicarboxylate (12c):** A solution of diazo compound **9b** (1.15 g, 3.46 mmol, 1 equiv.) in hexane (60 mL) was added with a syringe pump (10 mL/h) to a refluxing solution of freshly distilled *N*-methoxycarbonylpyrrole (0.97 mL, 8.65 mmol, 2.5 equiv.) and $Rh_2(OOct)_4$ (27 mg, 34.6 µmol, 1 mol-%) in hexane (60 mL). At the end of the addition, the refluxed was maintained for 1 h. After cooling, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 1:8 to 1:7) to afford the desired cycloadduct **12c** (760 mg, 51 %) as a yellow oil. $R_f$ = 0.16 (EtOAc/cyclohexane, 1:8). $^1$H NMR, COSY (300 MHz, $CDCl_3$): $\delta$ = 7.42–7.27 (m, 5 H, Ph), 6.54–6.44 (m, 1 H, 7-H), 5.96–5.86 (m, 1 H, 6-H), 5.35–5.13 (m, 3 H, 1-H, $CH_2$Ph), 4.78–4.66 (m, 1 H, 5-H), 3.67 (s, 3 H, $CO_2CH_3$), 2.95–2.65 (m, 1 H, 4-$H_a$), 1.86 (d, $J$ = 17.9 Hz, 1 H, 4-$H_b$), 0.88 [s, 9 H, $C(CH_3)_3$], 0.13 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$) ppm. $^{13}$C NMR, HSQC, HMBC (75 MHz, $CDCl_3$): $\delta$ = 164.5 ($CO_2$Bn), 159.0 (C-3), 154.2 ($NCO_2$Me), 138.4 (C-7), 136.6 (Cq-Ar), 128.6 (3 CH-Ar), 128.2 (CH-Ar), 128.1 (CH-Ar), 127.5 (C-6), 115.0 (C-2), 65.7 ($CH_2$Ph), 56.5 (C-5), 56.3 (C-1), 52.7 ($OCH_3$), 33.2 (C-4), 25.8 [$C(CH_3)_3$], 18.6 [$C(CH_3)_3$], –3.5 ($SiCH_3$), –3.6 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 1706, 1193, 839 cm$^{-1}$. HRMS (ESI) $m/z$ 452.1864 ([M + Na]$^+$, calcd. for $C_{23}H_{31}NO_5SiNa$ 451.1869).

**8-*tert*-Butyl 2-Methyl 3-Oxo-8-azabicyclo[3.2.1]oct-6-ene-2,8-dicarboxylate (7a):** TBAF (1 M in THF, 0.44 mL, 0.436 mmol, 1.5 equiv.) was added to a solution of silyl enol ether **12a** (115 mg, 0.291 mmol, 1 equiv.) in THF (0.5 mL) at 0 °C. The solution was stirred at room temp. for 1 h. Sat. aq. $NH_4Cl$ (1 mL) was then added and the product was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 1:3) to afford the desired keto ester **7a** (60 mg, 74 %) as an orange oil. $R_f$ = 0.28 (EtOAc/cyclohexane, 1:3). $^1$H NMR, COSY (400 MHz, $CDCl_3$): $\delta$ = 6.56–6.45 (m, 0.6 H, 7-H dia 1), 6.36–6.16 (m, 1.4 H, 7-H, dia 2, 6-H), 5.19 (s, 0.4 H, 1-H or 5-H, dia 2), 5.05–4.69 (m, 1.6 H, 1-H, 5-H), 3.86–3.58 (m, 3.6 H, $OCH_3$, 2-H, dia 1), 3.27 (s, 0.4 H, 2-H, dia 2), 2.98 (dd, $J$ = 16.1, 4.3 Hz, 0.4 H, 4-$H_a$, dia 2), 2.83–2.54 (m, 0.6 H, 4-$H_a$, dia 1), 2.47–2.34 (m, 1 H, 4-$H_b$), 1.50 [s, 5.4 H, $C(CH_3)_3$, dia 1], 1.47 [s, 5.4 H, $C(CH_3)_3$, dia 2] ppm. Spectroscopic data are in accordance with the literature.[15]

**Dimethyl 3-Oxo-8-azabicyclo[3.2.1]oct-6-ene-2,8-dicarboxylate (7b):** TBAF (1 M in THF, 1.7 mL, 1.73 mmol, 1.5 equiv.) was added to a solution of silyl enol ether **12b** (408 mg, 1.15 mmol, 1 equiv.) in THF (2.0 mL) at 0 °C. The solution was stirred at room temp. for 1 h. Sat. aq. $NH_4Cl$ (2 mL) was then added and the product was extracted with EtOAc (6 × 4 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 1:2 to 1:1) to afford the desired keto ester **7b**

(258 mg, 94 %) as a yellow oil. $R_f$ = 0.21 (EtOAc/cyclohexane, 1:2). $^1$H NMR, COSY (400 MHz, $CDCl_3$, 323 K): $\delta$ = 6.51 (dd, $J$ = 6.2, 2.5 Hz, 0.5 H, 7-H, dia 1), 6.30 (dd, $J$ = 6.1, 2.4 Hz, 0.5 H, 6-H, dia 2), 6.25 (dd, $J$ = 6.1, 2.5 Hz, 0.5 H, 6-H, dia 1), 6.22 (dd, $J$ = 6.0, 2.5 Hz, 0.5 H, 7-H, dia 2), 5.24–5.16 (br. s, 0.5 H, 1-H, dia 2), 5.00–4.95 (br. s, 0.5 H, 1-H, dia 1), 4.95–4.90 (br. s, 0.5 H, 5-H, dia 2), 4.89–4.82 (br. s, 0.5 H, 5-H, dia 1), 3.78 (s, 1.5 H, $OCH_3$), 3.76 (s, 1.5 H, $OCH_3$, dia 2), 3.72 (s, 1.5 H, $OCH_3$), 3.71 (s, 1.5 H, $OCH_3$, dia 1), 3.70–3.66 (m, 0.5 H, 2-H, dia 1), 3.26 (s, 0.5 H, 2-H, dia 2), 3.00 (dd, $J$ = 16.2, 4.4 Hz, 0.5 H, 4-$H_a$, dia 2), 2.76–2.62 (m, 0.5 H, 4-$H_a$, dia 1), 2.40 (dt, $J$ = 16.1, 1.3 Hz, 0.5 H, 4-$H_b$), 2.39 (dd, $J$ = 15.8, 1.6 Hz, 0.5 H, 4-$H_b$) ppm. $^{13}$C NMR, HSQC, HMBC (100 MHz, $CDCl_3$, 323 K): $\delta$ = 200.8 (C-3, dia 2), 199.6 (C-3, dia 1), 168.4 (CO, dia 1), 168.2 (CO, dia 2), 153.2 (NCO), 153.1 (NCO), 136.3 (C-6, dia 2), 134.3 (C-6, dia 1), 133.5 (C-7, dia 1), 132.7 (C-7, dia 2), 62.4 (C-2, dia 1), 60.3 (C-2, dia 2), 59.5 (C-1, dia 2), 58.3 (C-1, dia 1), 57.1 (C-5, dia 2), 56.6 (C-5, dia 1), 53.0 ($OCH_3$), 52.8 ($OCH_3$), 52.6 ($OCH_3$, dia 1), 52.3 ($OCH_3$, dia 2), 44.8 (C-4), 44.3 (C-4) ppm. IR (film): $\tilde{\nu}$ = 1738, 1701, 1450 cm$^{-1}$. HRMS (ESI) $m/z$ 262.0688 ([M + Na]$^+$, calcd. for $C_{11}H_{13}NO_5Na$ 262.0691).

**8-Methyl 2-Benzyl 3-Oxo-8-azabicyclo[3.2.1]oct-6-ene-2,8-dicarboxylate (7c):** TBAF (1 M in THF, 0.94 mL, 0.936 mmol, 1.5 equiv.) was added to a solution of silyl enol ether **12c** (268 mg, 0.624 mmol, 1 equiv.) in THF (1.1 mL) at 0 °C. The solution was stirred at room temp. for 1 h. Sat. aq. $NH_4Cl$ (2 mL) was then added and the product was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 1:3 to 1:2) to afford the desired keto ester **7c** (159 mg, 81 %) as a yellow oil. $R_f$ = 0.29 (EtOAc/cyclohexane, 1:2). $^1$H NMR, COSY (400 MHz, $CDCl_3$, 323 K): $\delta$ = 7.40–7.28 (m, 5 H, Ph), 6.48 (dd, $J$ = 6.2, 2.5 Hz, 0.5 H, 7-H, dia 1), 6.30 (dd, $J$ = 6.1, 2.4 Hz, 0.5 H, 6-H, dia 2), 6.24 (dd, $J$ = 6.1, 2.5 Hz, 0.5 H, 6-H, dia 1), 6.20 (dd, $J$ = 6.1, 2.5 Hz, 0.5 H, 7-H, dia 2), 5.27–5.25 (br. s, 0.5 H, 1-H, dia 2), 5.23 (d, $J$ = 12.3 Hz, 0.5 H, C$H_2$Ph, dia 1), 5.17 (d, $J$ = 12.3 Hz, 0.5 H, C$H_2$Ph, dia 1), 5.13 (s, 1 H, C$H_2$Ph, dia 2), 5.02–4.97 (br. s, 0.5 H, 1-H, dia 1) 4.97–4.91 (br. s, 0.5 H, 5-H, dia 2), 4.89–4.82 (br. s, 0.5 H, 5-H, dia 1), 3.78–3.74 (m, 0.5 H, 2-H, dia 1), 3.76 (s, 1.5 H, $CO_2CH_3$), 3.64 (s, 1.5 H, $CO_2CH_3$), 3.31 (s, 1 H, 0.5 H, 2-H, dia 2), 2.98 (dd, $J$ = 16.1, 4.4 Hz, 0.5 H, 4-$H_a$, dia 2), 2.76–2.61 (m, 0.5 H, 4-$H_a$, dia 1), 2.41 (d, $J$ = 16.2 Hz, 0.5 H, 4-$H_b$, dia 2), 2.39 (dd, $J$ = 15.9, 1.6 Hz, 0.5 H, 4-$H_b$, dia 1) ppm. $^{13}$C NMR, HSQC, HMBC (100 MHz, $CDCl_3$, 323 K): $\delta$ = 200.7 (C-3, dia 2), 199.5 (C-3, dia 1), 167.8 ($CO_2$Bn, dia 2), 167.6 ($CO_2$Bn, dia 1), 153.2 (N$CO_2CH_3$), 153.0 (N$CO_2CH_3$), 136.4 (C-6, dia 2), 135.6 (Cq-Ar, dia 1), 135.3 (Cq-Ar, dia 2), 134.2 (C-6, dia 1), 133.5 (C-7, dia 1), 132.7 (C-7, dia 2), 128.73 (CH-Ar), 128.68 (CH-Ar), 128.53 (CH-Ar), 128.44 (0.5 CH-Ar), 128.35 (0.5 CH-Ar), 128.30 (CH-Ar), 67.6 ($CH_2$Ph, dia 2), 67.2 ($CH_2$Ph, dia 1), 62.5 (C-2, dia 1), 60.4 (C-2, dia 2), 59.5 (C-1, dia 2), 58.3 (C-1, dia 1), 57.0 (C-5, dia 1), 56.6 (C-5, dia 2), 52.9 ($OCH_3$), 52.7 ($OCH_3$), 44.9 (C-4, dia 2), 44.3 (C-4, dia 1) ppm. IR (film): $\tilde{\nu}$ = 1737, 1703, 1450 cm$^{-1}$. HRMS (ESI) $m/z$ 338.1004 ([M + Na]$^+$, calcd. for $C_{17}H_{17}NO_5Na$ 338.1004).

***tert*-Butyl 3-Oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (13a):** A solution of β-keto ester **7a** (28 mg, 99.2 μmol, 1 equiv.), LiCl (11 mg, 0.248 mmol, 2.5 equiv.) and $H_2O$ (2 drops) in DMSO (0.82 mL) was heated at 130 °C for 1 h. After cooling, water (2 mL) was added and the product was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 1:5) to afford the *N*-Boc-6,7-dehydrotropinone **13a** (8 mg, 34 %) as an orange solid. $R_f$ = 0.35 (EtOAc/cyclohexane, 1:3). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.26–6.16 (m, 2 H, 6-H, 7-H), 4.88–4.69 (br. d, 2 H, 1-H, 5-H), 2.87–2.56 (m, 2 H, 2-$H_a$, 4-$H_a$), 2.36 (d, $J$ = 16.0 Hz, 2 H, 2-$H_b$, 4-$H_b$), 1.50 [s, 9 H, C$(CH_3)_3$] ppm. Spectroscopic data are in accordance with the literature.[36]

**Methyl 3-Oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (13b):** A solution of β-keto ester **7b** (51 mg, 0.213 mmol, 1 equiv.), LiCl (23 mg, 0.532 mmol, 2.5 equiv.) and $H_2O$ (2 drops) in DMSO (1.7 mL) was heated at 130 °C for 7 h. After cooling, water (3 mL) was added and the product was extracted with EtOAc (5 × 4 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 2:3) to afford the *N*-Moc-6,7-dehydrotropinone **13b** (16 mg, 41 %) as a white solid. $R_f$ = 0.39 (EtOAc/cyclohexane, 1:1), m.p. 68–70 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.29–6.17 (br. s, 2 H, 6-H, 7-H), 4.89–4.78 (br. d, 2 H, 1-H, 5-H), 3.77 (s, 3 H, $OCH_3$), 2.84–2.59 (m, 2 H, 2-$H_a$, 4-$H_a$), 2.39 (d, $J$ = 15.9 Hz, 2 H, 2-$H_b$, 4-$H_b$) ppm. Spectroscopic data are in accordance with the literature.[37]

**Methyl 3-Hydroxy-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (15):** L-Selectride® (1 M in THF, 0.19 mL, 0.188 mmol, 1.1 equiv.) was added dropwise to a solution of **13b** in THF (1.7 mL) at –78 °C. The solution was then stirred at room temp. for 50 min. After cooling to 0 °C, 1 M NaOH (0.58 mL) and 35 % aqueous $H_2O_2$ (0.58 mL) were added. The solution was stirred at room temp. for 15 min and 1 M HCl (0.58 mL) was added. The product was extracted with $CH_2Cl_2$ (3 × 2 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 2:1 to 4:1) to afford the alcohol **15** (24 mg, 75 %) as a pale yellow oil. $R_f$ = 0.19 (EtOAc/cyclohexane, 4:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.48–6.34 (br. s, 2 H, 6-H, 7-H), 4.70–4.52 (br. d, $J$ = 21.8 Hz, 2 H, 1-H, 5-H), 3.94 (tt, $J$ = 5.9, 1.0 Hz, 1 H, 3-H), 3.72 (s, 3 H, $OCH_3$), 2.35–2.11 (m, 2 H, 2-$H_a$, 4-$H_a$), 2.09–1.94 (br. s, 1 H, OH), 1.79 (dd, $J$ = 15.1, 1.3 Hz, 2 H, 2-$H_b$, 4-$H_b$) ppm. Spectroscopic data are in accordance with the literature.[38]

**6-Hydroxytropinone (16):** 2,5-Dihydro-2,5-dimethoxyfuran (1.20 mL, 9.89 mmol, 1 equiv.) was added to 3 N aq. HCl (18 mL). The solution was stirred at room temp. for 15 h. The solution was then neutralized using 6 M aq. NaOH (≈ 8 mL) and stirred for 30 min. This solution was added to a solution of NaOAc·3$H_2O$ (5.65 g, 41.6 mmol, 4.2 equiv.), $MeNH_2$·HCl (735 mg, 10.9 mmol, 1.1 equiv.) and 3-oxoglutaric acid (1.59 g, 10.9 mmol, 1.1 equiv.) in $H_2O$ (69 mL). The solution was stirred at room temp. for 5 d. $K_2CO_3$ (7.4 g) and NaCl (7.4 g) were added and the solution was stirred at room temp. for 45 min. The product was extracted with $CHCl_3$ (12 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (MeOH/$CH_2Cl_2$, 1:99 to 3:97 + 10 % $Et_3N$) to afford hydroxytropinone **15** (450 mg, 30 %) as a brown solid. An analytical sample of **16** was purified by recrystallization in *i*PrOH to obtain the spectroscopic data. $R_f$ = 0.36 (MeOH/$CH_2Cl_2$, 5:95 + 10 % $Et_3N$), m.p. 120–121 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.07 (d, $J$ = 5.5 Hz, 1 H, 6-H), 3.63–3.56 (m, 1 H, 1-H or 5-H), 3.38 (d, $J$ = 5.2 Hz, 1 H, 1-H or 5-H), 2.74–2.61 (m, 2 H, 2-$H_a$, 4-$H_a$), 2.66 (s, 3 H, $CH_3$), 2.24–2.13 (m, 2 H, 2-$H_b$ or 4-$H_b$, OH), 2.13–1.94 (m, 3 H, 2-$H_b$ or 4-$H_b$, 7-H) ppm. Spectroscopic data are in accordance with the literature.[39]

**8-Methyl-8-azaspiro[bicyclo[3.2.1]octane-3,2′-[1,3]dioxolan]-6-ol (20):** *p*TsOH·$H_2O$ (244 mg, 1.28 mmol, 1.1 equiv.) was added to a solution of hydroxytropinone **16** (181 mg, 1.17 mmol, 1 equiv.) and ethylene glycol (0.65 mL, 11.7 mmol, 10 equiv.) in benzene (5.5 mL). The solution was refluxed with a Dean–Stark trap for 3 h. After cooling, $Na_2CO_3$ (366 mg) and brine (11 mL) were added. The product was extracted with $CHCl_3$ (6 × 10 mL). The combined or-

ganic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (MeOH/$CH_2Cl_2$, 3:97 to 5: 95 + 10 % $Et_3N$) to afford the desired acetal **20** (210 mg, 90 %) as a brown solid. $R_f$ = 0.38 (MeOH/$CH_2Cl_2$, 5:95 + 10 % $Et_3N$), m.p. 91–93 °C. $^1H$ NMR, COSY (300 MHz, $CDCl_3$): $\delta$ = 4.40 (dd, $J$ = 7.4, 2.5 Hz, 1 H, 6-H), 3.94–3.86 (m, 2 H, $OCH_2CH_2O$), 3.82–3.74 (m, 2 H, $OCH_2CH_2O$), 3.35–3.27 (m, 1 H, 1-H), 3.10–3.04 (m, 1 H, 5-H), 2.58–2.45 (m, 1 H, 7-$H_a$), 2.50 (s, 3 H, $CH_3$), 2.09–1.98 (m, 2 H, 2-$H_a$, 4-$H_a$), 1.81–1.70 (m, 1 H, 7-$H_b$), 1.59 (dt, $J$ = 14.3, 2.3 Hz, 1 H, 4-$H_b$), 1.43 (dt, $J$ = 14.2, 2.3 Hz, 1 H, 2-$H_b$) ppm. $^{13}C$ NMR, HSQC, HMBC (75 MHz, $CDCl_3$): $\delta$ = 106.5 (C-3), 74.9 (C-6), 67.4 (C-5), 64.3 ($OCH_2$), 63.2 ($OCH_2$), 58.7 (C-1), 40.4 (C-7), 35.0 ($NCH_3$), 34.5 (C-2), 33.1 (C-4) ppm. IR (film): $\tilde{\nu}$ = 3367, 2936 $cm^{-1}$. HRMS (ESI) $m/z$ 200.1293 ([M + H]$^+$, calcd. for $C_{10}H_{18}NO_3$ 200.1287).

**8-Methyl-8-azaspiro[bicyclo[3.2.1]octane-3,2′-[1,3]dioxolan]-6-yl 4-Methylbenzenesulfonate (21):** DMAP (15 mg, 0.126 mmol, 0.1 equiv.) followed by $Et_3N$ (0.23 mL, 1.63 mmol, 1.3 equiv.) and TsCl (311 mg, 1.63 mmol, 1.3 equiv.) were added to a solution of alcohol **20** (250 mg, 1.26 mmol, 1 equiv.) in $CH_2Cl_2$ (5.4 mL). The solution was stirred at room temp. for 26 h before DMAP (15 mg, 0.126 mmol, 0.1 equiv.), $Et_3N$ (0.23 mL, 1.63 mmol, 1.3 equiv.) and TsCl (311 mg, 1.63 mmol, 1.3 equiv.) were added. The solution was stirred for 17 h. Water (5 mL) was then added and the product was extracted with $CH_2Cl_2$ (3 × 6 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 3:1 + 10 % $Et_3N$) to afford the tosylate **21** (413 mg, 93 %) as a yellow oil. $R_f$ = 0.45 (EtOAc/cyclohexane, 6:1 + 10 % $Et_3N$). $^1H$ NMR, COSY (400 MHz, $CDCl_3$): $\delta$ = 7.78 (d, $J$ = 8.3 Hz, 2 H, CH-Ar), 7.33 (d, $J$ = 8.3 Hz, 2 H, CH-Ar), 5.31 (dd, $J$ = 7.5, 2.8 Hz, 1 H, 6-H), 3.94–3.84 (m, 2 H, $OCH_2CH_2O$), 3.83–3.74 (m, 2 H, $OCH_2CH_2O$), 3.33–3.28 (m, 1 H, 1-H), 3.38–3.24 (br. s, 1 H, 5-H), 2.48–2.40 (m, 1 H, 7-$H_a$), 2.44 (s, 3 H, $NCH_3$ or Cq-$CH_3$), 2.43 (s, 3 H, $NCH_3$ or Cq-$CH_3$), 2.08–1.92 (m, 3 H, 2-$H_a$, 4-$H_a$, 7-$H_b$), 1.67–1.60 (m, 1 H, 4-$H_b$), 1.53–1.45 (m, 1 H, 2-$H_b$) ppm. $^{13}C$ NMR, HSQC, HMBC (100 MHz, $CDCl_3$): $\delta$ = 144.7 [Cq-Ar($CH_3$)], 134.5 (Cq-Ar), 129.9 (2 CH-Ar), 127.9 (2 CH-Ar), 106.3 (C-3), 85.8 (C-6), 65.9 (C-5), 64.5 ($OCH_2$), 63.5 ($OCH_2$), 59.8 (C-1), 37.8 ($NCH_3$), 37.5 (C-2), 36.4 (C-4), 36.3 (C-7), 21.8 (C-12) ppm. IR (film): $\tilde{\nu}$ = 2934, 1190, 1097, 925 $cm^{-1}$. HRMS (ESI) $m/z$ 354.1387 ([M + H]$^+$, calcd. for $C_{17}H_{24}NO_5S$ 354.1375).

**8-Methyl-8-azaspiro[bicyclo[3.2.1]oct[6]ene-3,2′-[1,3]dioxolane] (22):** $t$BuOK (1 M in THF, 2.6 mL, 2.63 mmol, 2.5 equiv.) was added to a solution of tosylate **21** (372 mg, 1.05 mmol, 1 equiv.) in THF (6.2 mL). The solution was stirred at room temp. for 6 h. Water (5 mL) was added and the product was extracted with $CH_2Cl_2$ (7 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 4:1 to 6:1 + 10 % $Et_3N$) to afford alkene **22** (174 mg, 91 %) as a yellow oil. $R_f$ = 0.33 (EtOAc/cyclohexane, 6:1 + 10 % $Et_3N$). $^1H$ NMR, COSY (400 MHz, $CDCl_3$): $\delta$ = 5.98 (s, 2 H, 6-H, 7-H), 3.87–3.81 (m, 2 H, $OCH_2CH_2O$), 3.76–3.71 (m, 2 H, $OCH_2CH_2O$), 3.48–3.43 (m, 2 H, 1-H, 5-H), 2.23 (s, 3 H, $NCH_3$), 2.12 (dd, $J$ = 13.9, 3.6 Hz, 2 H, 2-$H_a$, 4-$H_a$), 1.78 (dt, $J$ = 12.8, 2.0 Hz, 2 H, 2-$H_b$, 4-$H_b$) ppm. $^{13}C$ NMR, HSQC, HMBC (100 MHz, $CDCl_3$): $\delta$ = 131.3 (C-6, C-7), 106.9 (C-3), 65.6 (C-1, C-5), 64.2 ($OCH_2$), 63.2 ($OCH_2$), 40.9 ($NCH_3$), 40.4 (C-2, C-4) ppm. IR (film): $\tilde{\nu}$ = 2933, 1083 $cm^{-1}$. HRMS (ESI) $m/z$ 182.1173 ([M + H]$^+$, calcd. for $C_{10}H_{16}NO_2$ 182.1181).

**6,7-Dehydrotropine (4):** 6 M aq. HCl (1 mL) was added to a solution of acetal **20** (153 mg, 0.841 mmol, 1 equiv.) in THF (1 mL). The solution was stirred at room temp. for 16 h. $K_2CO_3$ was then added (pH ≈ 8–9) and the product was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude ketone obtained was used without further purification. L-Selectride® (1 M in THF, 0.93 mL, 0.926 mmol, 1.1 equiv.) was added dropwise to a solution of previously formed ketone in THF (8.5 mL) at –78 °C. The solution was then stirred at room temp. for 1 h. After cooling to 0 °C, water (0.11 mL) and 35 % aqueous $H_2O_2$ (0.21 mL) were added. Saturated aqueous $Na_2SO_3$ (2 mL) was added. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 mL) and the combined aqueous layer was extracted with $CHCl_3$ (8 × 4 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (MeOH/$CHCl_3$, 5:95 + 10 % $Et_3N$) to afford alcohol **4** (62 mg, 53 %) as a pale yellow oil. $R_f$ = 0.30 (MeOH/$CH_2Cl_2$, 5:95 + 10 % $Et_3N$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.25 (s, 2 H, 6-H, 7-H), 3.90 (t, $J$ = 6.0 Hz, 1 H, 3-H), 3.57–3.51 (br. s, 2 H, 1-H, 5-H), 2.41–2.32 (m, 5 H, 2-$H_a$, 4-$H_a$, $CH_3$), 1.84 (d, $J$ = 14.1 Hz, 2 H, 2-$H_b$, 4-$H_b$) ppm. $^{13}C$ NMR, HSQC, HMBC (100 MHz, $CDCl_3$): $\delta$ = 134.0 (C-6, C-7), 66.4 (C-1, C-5), 65.0 (C-3), 41.4 ($CH_3$), 37.1 (C-2, C-4) ppm. IR (film): $\tilde{\nu}$ = 3357, 3324, 1073, 1044 $cm^{-1}$. HRMS (ESI) $m/z$ 140.1082 ([M + H]$^+$, calcd. for $C_8H_{14}NO$ 140.1075).

**8-Methyl-8-azabicyclo[3.2.1]oct-6-en-3-yl 3-Hydroxy-2-phenylpropanoate (24):** Water from $p$TsOH·$H_2O$ (145 mg, 0.762 mmol, 1 equiv.) was removed by coevaporation with benzene (2 × 3 mL). The dried $p$TsOH was then dissolved in $Et_2O$ (4.8 mL) and was added to a suspension of **4** (106 mg, 0.762 mmol, 1 equiv.) in $Et_2O$ (4.8 mL). The solution was stirred at room temp. for 40 min. The product was filtered, washed with dry $Et_2O$ (40 mL) and dried in vacuo to obtain the ammonium salt **21** (174 mg, 73 %) as a white solid which was used without further purification. $SOCl_2$ (0.11 mL, 1.48 mmol, 5.5 equiv.) was added to a solution of acetyltropic acid[40] (79 mg, 0.378 mmol, 1.4 equiv.) in benzene (0.30 mL). The solution was stirred at 65 °C for 2.5 h. After cooling, the solution was concentrated under reduced pressure. The crude product was dissolved in benzene (0.4 mL) and **21** (84 mg, 0.270 mmol, 1 equiv.) was added. The solution was refluxed for 4 h. After cooling, 6 M HCl (0.33 mL) was added and the reaction was stirred at room temp. for 13 h. $K_2CO_3$ was added (until pH 7–8) and the solution was diluted in a mixture of MeOH/$CHCl_3$ (1:1, 40 mL). The solution was filtered and concentrated under reduced pressure. The oil was dissolved in a mixture of MeOH/$CHCl_3$ (1:5). The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography with alumina (MeOH/$CHCl_3$, 1:100) to afford a mixture of ester **24** and alcohol **4** (71.5 mg, 84 %wt of **24**, 56 % over the two steps) as a pale yellow oil. Separation was carried out in the subsequent step. $R_f$ = 0.25 (MeOH/$CHCl_3$, 1:100, neutral $Al_2O_3$). $^1H$ NMR, COSY (300 MHz, $CDCl_3$): $\delta$ = 7.38–7.18 (m, 5 H, Ph), 6.22 (s, 0.75 H, 6′-H, 7′-H), 5.79 (dd, $J$ = 5.6, 1.9 Hz, 1 H, 6-H or 7-H), 5.40 (dd, $J$ = 5.6, 1.9 Hz, 1 H, 6-H or 7-H), 4.98 (t, $J$ = 6.1 Hz, 1 H, 3-H), 4.10 (dd, $J$ = 10.9, 8.6 Hz, 1 H, 9-$H_a$), 3.87–3.66 (m, 2.38 H, 3′-H, 8-H, 9-$H_b$), 3.42 (t, $J$ = 2.8 Hz, 0.75 H, 1′-H, 5′-H), 3.32 (dt, $J$ = 4.0, 2.2 Hz, 1 H, 1-H or 5-H), 3.22 (dt, $J$ = 4.0, 2.2 Hz, 1 H, 1-H or 5-H), 2.27–2.05 (m, 2.75 H, 2′-$H_a$, 4′-$H_a$, 2-$H_a$, 4-$H_a$), 2.24 (s, 1.13 H, $CH_3$), 2.19 (s, 3 H, $CH_3$), 1.79 (d, $J$ = 13.5 Hz, 0.75 H, 2′-$H_b$, 4′-$H_b$), 1.66 (dt, $J$ = 14.9, 2.2 Hz, 1 H, 2-$H_b$ or 4-$H_b$), 1.49 (dt, $J$ = 15.0, 2.1 Hz, 1 H, 2-$H_b$ or 4-$H_b$) ppm. $^{13}C$ NMR, HSQC, HMBC (75 MHz, $CDCl_3$): $\delta$ = 172.0 (CO), 136.1 (Cq-Ar), 134.5 (C-6′, C-7′), 131.64 (C-6 or C-7), 131.60 (C-6 or C-7), 128.8 (2 CH-Ar), 128.4 (2 CH-Ar), 127.7 (CH-Ar), 67.8 (C-3), 66.1 (C-1′, C-5′), 65.40 (C-1 or C-5), 65.38 (C-3′), 65.3 (C-1 or C-5), 64.2 (C-9), 54.5 (C-8), 41.7 ($CH_3$), 41.5 ($CH_3$), 37.6 (C-2′, C-4′), 33.6 (C-2 or C-4), 33.5 (C-2 or C-4) ppm. IR (film): $\tilde{\nu}$ = 3368, 2937, 1724, 1170, 1037 $cm^{-1}$. HRMS (ESI) $m/z$ 288.1597 ([M + H]$^+$, calcd. for $C_{17}H_{22}NO_3$ 288.1600).

**Scopolamine (2):** 35 % aq. $H_2O_2$ (0.1 mL) was added to a solution of **24** (16.7 mg, 58.1 μmol, 1 equiv.) in formic acid (0.1 mL). The solution was stirred at room temp. for 1 d. A second portion of 35 % aq. $H_2O_2$ (0.1 mL) was added and the solution was stirred at room temp. for 2 d. Sat. aq. $Na_2SO_3$ and $CHCl_3$ were added. 2 M NaOH was then added (until pH 8–9) and the product was extracted with $CHCl_3$ (3 × 2 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on alumina (MeOH/$CHCl_3$, 0.5:100 to 1:100) to afford **2** (2.8 mg, 16 %) as a pale yellow oil. $R_f$ = 0.25 (EtOAc/cyclohexane, 1:3 + 10 % $Et_3N$). $^1H$ NMR, COSY, NOESY (400 MHz, $CDCl_3$): $\delta$ = 7.39–7.19 (m, 5 H, Ph), 5.04 (t, $J$ = 5.5 Hz, 1 H, 3-H), 4.17 (dd, $J$ = 11.1, 8.9 Hz, 1 H, 9-$H_a$), 3.82 (dd, $J$ = 11.1, 5.2 Hz, 1 H, 9-$H_b$), 3.75 (dd, $J$ = 8.9, 5.1 Hz, 1 H, 8-H), 3.38 (d, $J$ = 3.0 Hz, 1 H, 6-H or 7-H), 3.12 (s, 1 H, 1-H or 5-H), 2.98 (s, 1 H, 1-H or 5-H), 2.64 (d, $J$ = 3.0 Hz, 1 H, 6-H or 7-H), 2.47 (s, 3 H, $CH_3$), 2.36–2.20 (m, 1 H, OH), 2.20–2.08 (m, 1 H, 2-$H_a$ or 4-$H_a$), 2.08–1.96 (m, 1 H, 2-$H_a$ or 4-$H_a$), 1.65–1.58 (m, 1 H, 2-$H_b$ or 4-$H_b$), 1.34 (d, $J$ = 15.2 Hz, 1 H, 2-$H_b$ or 4-$H_b$) ppm. Spectroscopic data are in accordance with the literature.[41]

**9-Methyl-3-oxa-9-azatricyclo[3.3.1.0$^{2,4}$]nonan-7-yl 3-[(*tert*-Butyldimethylsilyl)oxy]-2-phenylpropanoate (26):** TBSCl (42 mg, 0.279 mmol, 1.2 equiv.) and imidazole (27 mg, 0.396 mmol, 1.7 equiv.) were added to a solution of **24** (49 mg, 0.171 mmol, 1 equiv.) in $CH_2Cl_2$ (2.3 mL). The solution was stirred at room temp. for 16 h. Water (2 mL) was added and the product was extracted with $CH_2Cl_2$ (3 × 2 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 1:3 + 10 % $Et_3N$) to afford the TBS-protected olefin **25** (47 mg, 68 %) as a pale yellow oil. $R_f$ = 0.27 (EtOAc/cyclohexane, 1:3 + 10 % $Et_3N$). $^1H$ NMR, COSY (600 MHz, $CDCl_3$): $\delta$ = 7.34–7.24 (m, 5 H, Ph), 5.88 (dd, $J$ = 5.5, 1.9 Hz, 1 H, 6-H or 7-H), 5.65 (dd, $J$ = 5.6, 1.9 Hz, 1 H, 6-H or 7-H), 4.98 (t, $J$ = 6.1 Hz, 1 H, 3-H), 4.16 (t, $J$ = 9.4 Hz, 1 H, 8-H), 3.76 (dd, $J$ = 9.7, 5.6 Hz, 1 H, 9-$H_a$), 3.67 (dd, $J$ = 9.1, 5.6 Hz, 1 H, 9-$H_b$), 3.35 (s, 1 H, 1-H or 5-H), 3.28 (s, 1 H, 1-H or 5-H), 3.24 (s, 3 H, $CH_3$), 2.23–2.18 (m, 1 H, 2-$H_a$ or 4-$H_a$), 2.14 (ddd, $J$ = 14.9, 6.1, 3.5 Hz, 1 H, 2-$H_a$ or 4-$H_a$), 1.69 (d, $J$ = 14.9 Hz, 1 H, 2-$H_b$ or 4-$H_b$), 1.56 (d, $J$ = 14.9 Hz, 1 H, 2-$H_b$ or 4-$H_b$), 0.85 [s, 9 H, SiC($CH_3$)$_3$], 0.01 (s, 3 H, Si$CH_3$), 0.00 (s, 3 H, Si$CH_3$) ppm. $^{13}C$ NMR, HSQC, HMBC (150 MHz, $CDCl_3$): $\delta$ = 171.5 (CO), 136.3 (Cq-Ar), 131.72 (C-6 or C-7), 131.67 (C-6 or C-7), 128.6 (2 CH-Ar), 128.4 (2 CH-Ar), 127.6 (CH-Ar), 67.4 (C-3), 65.6 (C-1 or C-5), 65.5 (C-1 or C-5), 65.3 (C-8), 55.2 (C-9), 41.7 ($CH_3$), 33.9 (C-2 or C-4), 33.6 (C-2 or C-4), 25.9 [SiC($CH_3$)$_3$], 18.4 [Si*C*($CH_3$)$_3$], –5.3 (Si$CH_3$), –5.4 (Si$CH_3$) ppm. $V_2O_5$ (3 mg) and 35 % aq. $H_2O_2$ (0.64 mL) were added to a solution of **25** (21 mg, 52.5 μmol, 1 equiv.) in $CH_3CN$ (0.8 mL). The solution was stirred at 45 °C for 20 h. After cooling, the solution was then concentrated under reduced pressure. Sat. aq. $K_2CO_3$ (2 mL) was added and the product was extracted with $CHCl_3$ (4 × 2 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane, 1:7 + 10 % $Et_3N$) to afford title compound **26** (8.6 mg, 39 %) as a pale yellow oil. $R_f$ = 0.63 (EtOAc/cyclohexane, 1:3 + 10 % $Et_3N$). $^1H$ NMR, COSY (600 MHz, $CDCl_3$): $\delta$ = 7.35–7.25 (m, 5 H, Ph), 5.00 (t, $J$ = 5.5 Hz, 1 H, 3-H), 4.18 (t, $J$ = 9.5 Hz, 1 H, 9-$H_a$), 3.78 (dd, $J$ = 9.8, 5.5 Hz, 1 H, 9-$H_b$), 3.70 (dd, $J$ = 9.2, 5.5 Hz, 1 H, 8-H), 3.50 (d, $J$ = 3.0 Hz, 1 H, 6-H or 7-H), 3.17–3.12 (br. s, 1 H, 1-H or 5-H), 3.10 (d, $J$ = 3.0 Hz, 1 H, 6-H or 7-H), 3.07–3.02 (br. s, 1 H, 1-H or 5-H), 2.49 (s, 3 H, $CH_3$), 2.15–2.08 (m, 1 H, 2-$H_a$ or 4-$H_a$), 2.08–1.99 (m, 1 H, 2-$H_a$ or 4-$H_a$), 1.65–1.60 (m, 1 H, 2-$H_b$ or 4-$H_b$), 1.46–1.38 (m, 1 H, 2-$H_b$ or 4-$H_b$), 0.86 [s, 9 H, C($CH_3$)$_3$], 0.03 (s, 3 H, Si$CH_3$), 0.01 (s, 3 H, Si$CH_3$) ppm. $^{13}C$ NMR, HSQC, HMBC (150 MHz, $CDCl_3$): $\delta$ = 171.3 (CO), 135.9 (Cq-Ar), 128.9 (2 CH-Ar), 128.2 (2 CH-Ar), 127.7 (CH-Ar), 65.7 (C-3), 65.2 (C-9), 58.1 (C1, C-5), 56.7 (C-6 or C-7), 56.4 (C-6 or C-7), 55.2 (C-8), 42.3 ($NCH_3$), 31.2 (C-2 or C-4), 30.9 (C-2 or C-4), 26.0 [C($CH_3$)$_3$], 18.4 [*C*($CH_3$)$_3$], –5.3 (Si$CH_3$), –5.4 (Si$CH_3$) ppm. IR (film): $\tilde{\nu}$ = 2928, 1732, 837 cm$^{-1}$. HRMS (ESI) *m/z* 418.2424 ([M + H]$^+$, calcd. for $C_{23}H_{36}NO_4Si$ 418.2414).

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