The Kulinkovich Reaction on Lactones. A Convenient Approach to Functionalized Cyclopropanols

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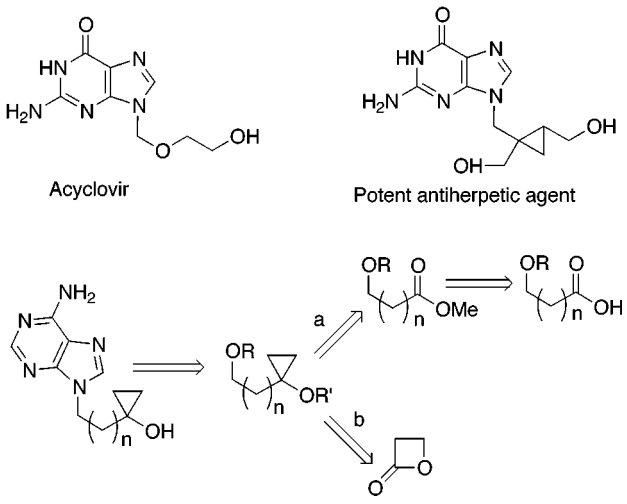
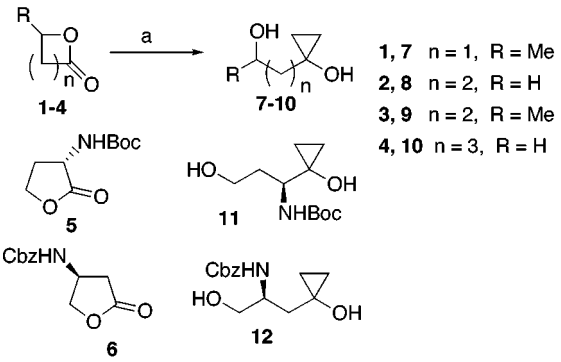
Cyclopropane-containing molecules are extremely important compounds for their biological properties, their natural occurrence, and their synthetic utility.[1] In the field of cyclopropane-containing drugs, cyclopropyl nucleosides has been found to have interesting properties as antiviral or antitumor agents.[2] Very recently a new compound with geminal disubstitution has been prepared and shows to be much superior to acyclovir as an antiherpetic agent.[3] This finding stimulated the research of new related structures and new synthetic methods.[4] Following our interest in the synthesis of differently functionalized nucleosides,[5] we were looking to prepare new structures having a cyclopropane, a OH group, and a nucleobase, as the product described in Scheme 1. A possible retrosynthetic analysis for these compounds suggests the introduction of the nucleobase by nucleophilic substitution on a mesylate or by Mitsunobu reaction with an alcohol and the construction of the cyclopropanol through the transformation of an ester function with the procedure described by Kulinkovich.[6]

A possible approach would be to start from differently substituted hydroxy acids and (1) make the *O*-protected ester; (2) perform the Kulinkovich reaction; (3) orthogonally protect the newly formed OH; (4) deprotect the other OH and eventually transform it into a leaving group; (5) perform the nucleophilic substitution or the Mitsunobu with a suitably protected nucleobase; and (6) finally deprotect the other OH. At least five or six steps altogether were needed for a simple molecule. Thus we envisaged lactones as potential substrates for the Kulinkovich reaction. In this case we would obtain directly a cyclopropyl diol that could be selectively functionalized on the more reactive primary or secondary OH (route b in Scheme 1).

Scheme 1



Scheme 2[a]



[a] (a) EtMgBr, Ti(O*i*-Pr)$_4$, THF/Et$_2$O, 70−80% yield.

Although well established, the Kulinkovich reaction has been carried out on esters[7] or disubstituted amides.[8]

We report here that differently substituted *β*-, *γ*-, and *δ*-lactones can be easily transformed into the corresponding *β*-, *γ*-, and *δ*-cyclopropyl diols following a slightly modified Kulinkovich procedure. First, we tried the reaction on simple lactones (**1**−**4** in Scheme 2) that reacted with 2.5 equiv of EtMgBr and 0.2 equiv of Ti(O*i*-Pr)$_4$ according to the general mechanism proposed[9] to give the desired diols **7**−**9** in 60−70% yields.

The last step with esters is the migration of the OMe group to titanium. With lactones, the ring opening probably occurs with formation of a spirocyclic alkoxy titanium derivative that is finally hydrolyzed by the NH_4-Cl solution to the diol (Scheme 3).

It was very important that the solvent of the reaction was a mixture of THF and Et$_2$O in a 8:2 ratio,[10] as in the presence of less THF, a green precipitate was observed with the formation of byproducts.[11] As described in Scheme 2, the reaction was successfully carried out also

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(1) Salaün, J. Rearrangements involving the cyclopropyl group. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z. Ed.; John Wiley and Sons: New York, 1987; 809. (b) Carbocyclic Three and Four-memebred Ring Systems. In *Methods of Organic Chemistry*; Houben-Weyl; de Meijere, A., Ed.; Thieme: Stuttgart New York, 1997; vol. 17a−f. (c) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511.

(2) Katagiri, N.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 3184. Nishiyama, S.; Ueki, S.; Watanabe, T.; Yamamura, S.; Kato, K.; Takita, T. *Tetrahedron Lett.* **1991**, *32*, 2141. Norbeck, D. W.; Sham, H. L.; Herrin, T.; Rosenbrook, W.; Plattner, J. J. *J. Chem. Soc., Chem. Commun.* **1992**, 128. Maag, H.; Nelson, J. T.; Steiner, J. L. R.; Prisbe, E. J. *J. Med. Chem.* **1994**, *37*, 431.

(3) Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 1284.

(4) See for example: Rifé, J.; Ortuño, R. M. *Org. Lett.* **1999**, *1*, 1221 and references therein.

(5) Esposito, A.; Taddei, M. *Nucleosides Nucleotides* **1999**, *18*, 985. Esposito, A.; Perino, M. G.; Taddei, M. *Eur. J. Org. Chem.* 1**999**, 931.

(6) Kulinkovich, O. G. *Russ. Chem. Rev.* **1993**, *62*, 839.

(7) Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345. Lee, J.; Kang, C. H., Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. Two examples of the reductive coupling of a lactone with terminal alkenes following a Kulinkovich protocol have been described in Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198.

(8) Lee, J.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 1584. Chaplinski, V.; Winsel, H.; Kordes, M.; de Meijere, A. *Synlett* **1997**, 111.

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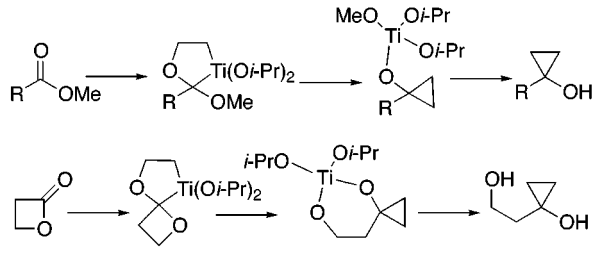
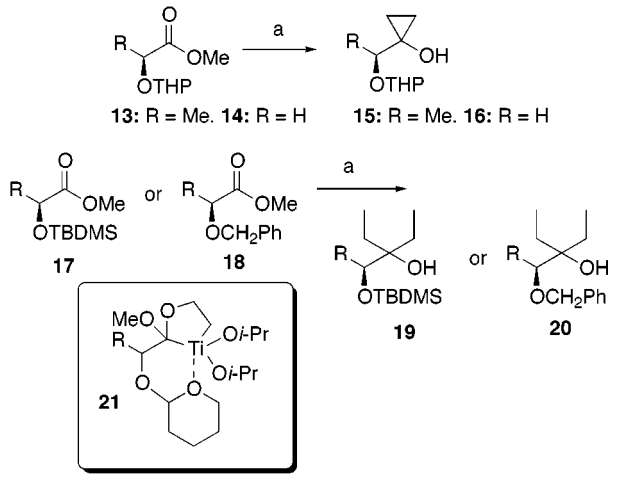
Scheme 3. Comparison of the Proposed Mechanism of the Kulinkovich Reaction on Esters with a Possible Mechanism on Lactones



Scheme 4[a]



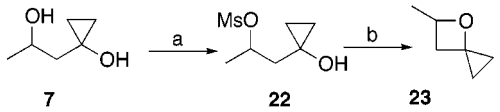
[a] (a) EtMgBr, $Ti(Oi\text{-}Pr)_4$, THF/Et_2O.

on 2-*N*-Boc and 3-*N*-Cbz 2-butyrolactones (**5** and **6**), prepared respectively from methionine and aspartic acid as previously reported.[12] From **5** and **6**, the *N*-protected amino cyclopropyl diols **11** and **12** were obtained, respectively, in 65 and 70% yields only when a large excess of $Ti(Oi\text{-}Pr)_4$ was used (see Experimental Section).

As α-lactones are not available, the precursors of a cyclopropyl alcohol with a nucleobase in the β position were prepared starting from (*S*)-methyl lactate or methyl glycolate protected as THP ethers (**13** or **14**). Also in these cases the Kulinkovich procedure worked well giving the desired products **15** and **16** in approximately 60% yield.

It is noteworthy that the reaction gave good results when THP was used as the protective group of hydroxy esters.[13] When the benzyl ether or the TBDMS ether was submitted to the Kulinkovich procedure, we obtained exclusively the products of addition of EtMgBr to the ester (**19** and **20** in Scheme 4). With TBDMS we interpreted the failure as a consequence of the steric hindrance, but the results with the benzyl ethers were not in accord with this conclusion. Probably the presence of a second oxygen atom on the substituent (THP) stabilizes

Scheme 5[a]



[a] (a) MsCl, Et_3N, 0 °C; (b) basic conditions.

the 1,3 oxatitanolane intermediate (**21** in Scheme 4) and promotes the cyclopropanation in favor of the simple Grignard reaction.

Compounds **7**−**10** (Scheme 3) have two OH groups that are expected to show a different reactivity. With electrophiles the less-hindered OH would react more rapidly than the cyclopropyl alcohol. With nucleophiles (after transformation to tosylates or mesylates or under Mitsunobu conditions) the OH on the cyclopropane ring would be less prone to react.

For this reason we first tried to transform compound **7** into the corresponding mono-mesylate and then perform a simple nucleophilic substitution with thymine. Unfortunately, while the mesylation occurred selectively on the less-hindered OH (1 equiv of MsCl at 0 °C in CH_2Cl_2) to give compound **22**, the next reaction with thymine in DMF and in the presence of Cs_2CO_3 gave always the spiro derivative **23** formed by an intramolecular cyclization. An analogous behavior was observed under the Mitsunobu conditions during the attempt to protect the OH of **22** with TBDMSCl in the presence of imidazole.To avoid a tedious series of protections of the primary (or secondary) alcohol, orthogonal protection of the cyclopropane OH, deprotection of the other OH, transformation to mesylate, nucleophilic substitution, and final deprotection, we decided to exploit the low reactivity to the nucleophilic substitution of a cyclopropylmesylate (Scheme 6).[14] As a model compound, **7** was transformed into the bis-mesylate **24** using 2.5 equiv of MsCl at room temperature in the presence of Et_3N, and this product was submitted to the reaction with thymine in DMF at 100 °C for 12 h in the presence of Cs_2CO_3. After filtration, evaporation of the DMF, and column chromatography on silica gel, we isolated compound **27** in 76% yield where the thymine substituted exclusively the secondary mesylate, and the cyclopropyl mesylate remained untouched, acting as an effective protecting group.[15] After purification, we isolated a single product with the thymine ring substituted exclusively at N1. The hydrolysis of the mesylate (deprotection) was finally accomplished with LiOH in refluxing water for 12 h. The nucleoside analogue **30** was isolated after selective extraction in EtOAc and further column chromatography on silica gel. Following this procedure with **8** and **9** as the starting materials, we isolated compounds **30**−**32** in 65−75% yields. The *N*-Cbz-cyclopropyl diol **12** was analogously bis-mesylated and further treated with thymine to give product **33** in 64% yield.

Adenine reacted with **24** or **25** to give, after deprotection of the mesylate, alcohols **34** or **35** in 65−70% yield.

(9) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskij, D. A. *Synthesis* **1991**, 234.

(10) Raiman, M. V.; Il'ina, N. A.; Kulinkovich, O. G. *Synlett* **1999**, 1053.

(11) The predominant component of the mixture was the product coming from the reaction of EtMgBr with the carbonyl of the lactone.

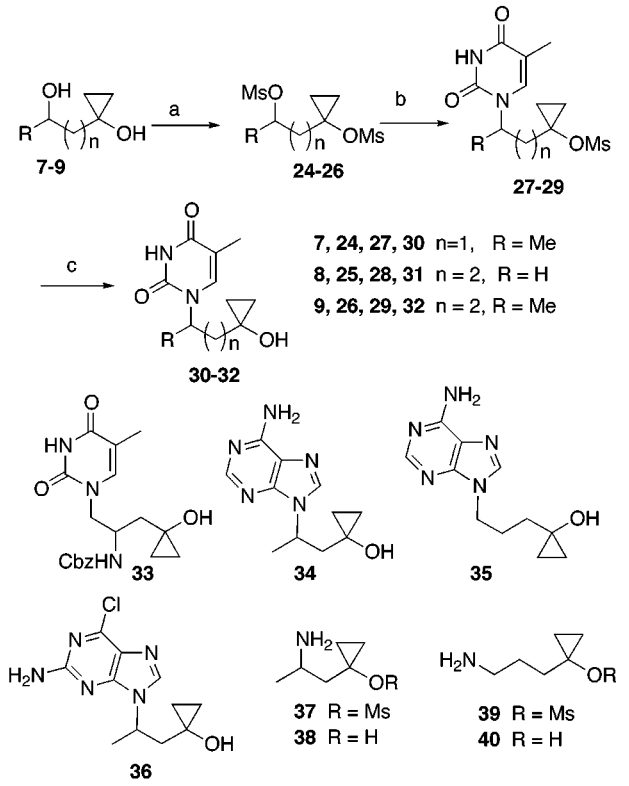
(12) For compound **5** see: Baldwin, J. E.; Flinn, A. *Tetrahedron Lett.* **1987**, *28*, 3605. For compound **6** see: Mcgarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943.

(13) Recently the transformation of an α-hydroxy ester into a cyclopropanol has been described using $ClTi(Oi\text{-}Pr)_3$: Cho, S. Y.; Cha, J. K. *Org. Lett.* **2000**, *2*, 1337.

(14) Gustavson, G. *J. Prakt. Chem.* **1891**, *43*, 369. Banert, K.; Bunse, M.; Engberty, T.; Gassen, K. R.; Kurnianto, A. W.; Kirmse, W. *Recl. J. R. Neth. Chem. Soc.* **1986**, *105*, 272. The explanation of the low reactivity of the cyclopropane ring to nucleophilic substitution is described in Brown, H. C.; Flechter, R. S.; Johannesen, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 212.

(15) However, methansulfonate is reported as a possible protection of alcohols in Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1991; p 117.

Scheme 6[a]



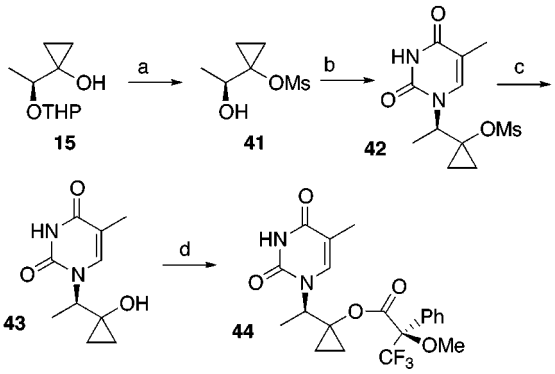
[a] (a) MsCl, Et_3N, CH_2Cl_2; (b) thymine, DMF, Cs_2CO_3, 100 °C; (c) LiOH, H_2O, reflux.

2-Chloro-6-aminopurine reacted with **24** to give compound **36 (**77% yield) that can be transformed to a guanine derivative by acidic hydrolysis. Although **34**−**36** were isolated as a single isomers from the substitution by the purine ring, we cannot exclude the formation of small amounts of the other regioisomers in the first step (the nucleophilic substitution of the mesylate). NaN_3 reacted with **24** and **25** to give the corresponding azido derivatives that were further submitted to reduction of the azido group (PPh_3 and NH_4Cl) to give compounds **37** and **39.** The mesylate group of **37** and **39** was immediately hydrolyzed following standard conditions to give amino alcohols **38** and **40** in 71 and 62% overall yield. Alternatively, the amino group of **37** and **39** can be transformed into a different heterocycle before hydrolysis.

Working on THP derivative **15** we experienced that the deprotection of the THP gave a mixture of products where the expected diol was not present.[16] Thus, compound **15** was transformed into the corresponding mesylate, and THP was removed under slightly acidic conditions to give compound **41** (Scheme 7)**.** The introduction of the thymine was carried out under Mitsunobu conditions affording mesylate **42** which was finally hydrolyzed to give compound **43** in 65% yield.

To test the possibility of racemization of the stereocenter present in the starting (*S*)-methyl lactate (used as 95:5 mixture of enantiomers) during the Kulinkovich reaction and the further synthetic steps, we transformed alcohol **43** into the corresponding (*R*)-MTPA ester **44**. ^{19}F

Scheme 7[a]



[a] (a) MsCl, Et_3N, CH_2Cl_2, and then *p*TsOH, MeOH. 80% yield; (b) thymine, PPh_3, DEAD, THF 40%; (c) LiOH, H_2O, 80 °C; (d) MTPACl, pyridine, $CDCl_3$.

NMR analysis showed the presence of the two diastereoisomers in a 91: 9 ratio, indicating a limited racemization.

Compounds prepared in Schemes 6 and 7 have been submitted for testing as potential antiviral agents.

In conclusion we have demonstrated that the Kulinkovich reaction can be carried out successfully on lactones or THP-protected hydroxy esters to give cyclopropyl diols and that the methanesulfonyl group can be conveniently used for the contemporary activation of the primary or secondary OH and for the protection of a tertiary (cyclopropyl) alcohol.

Experimental Section

Melting points were obtained in open capillary tubes and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ or DMSO-d_6 solutions. Mass spectra were recorded in the electron impact mode after introduction through a gas chromatographic capillary column. Column chromatographic purifications were performed with silica gel 60 (230−400 mesh). Solvents were at reagent grade and in many cases dried prior uses.[17]

Starting materials **5** and **6** were synthesized following the reported procedures.[12]

General Procedure for Preparation of Diols 7−10. 1-(2-Hydroxypropyl)cyclopropanol (7). To a solution of lactone **1** (1.7 g, 20 mmol) and Ti(Oi-Pr)$_4$ (1.18 mL, 4 mmol) in dry THF (60 mL), at 15° under N_2 atmosphere, was added EtMgBr (45 mmol, 15 mL) dropwise over 2 h. During the addition, the temperature of the reaction must be kept under 20 °C. After 2 h, the reaction was quenched by addition of a saturated NH_4Cl solution (50 mL). The water layer was extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The orange oily residue was purified on silica gel column with ethyl acetate as eluent, to give diol **7** as yellow oil (1.62 g, 70% yield). ^1H NMR ($CDCl_3$) δ 4.10 (m, 1 H), 2.23 (bs, 2H), 1.83 (m, 1H), 1.25 (m, 1H), 1.11 (d, J = 6 Hz, 3 H), 0.70−0.60 (m, 2 H), 0.41−0.24 (m, 2 H). ^{13}C δ NMR 63.4, 57.8, 50.3, 25.7, 14.2, 13.4. Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H,10.41. Found: C, 62.14; H,10.36.

1-(1-*tert*-(Butoxycarbonylamino)3-hydroxypropyl)cyclopropanol 11. General Procedure. To a solution of lactone **5** (0.56 g, 2.8 mmol) and Ti(O*i*-Pr)$_4$ (0.32 mL, 1.02 mmol) in dry THF (5.5 mL) at 15 °C under inert atmosphere was added EtMgBr (2.8 mL, 8.4 mmol) slowly. The mixture was stirred for 24 h, quenched with a saturated solution of NH_4Cl, and extracted with ethyl acetate. The separated organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The obtained crude oil was purified on silica gel column (eluent $CHCl_3$) to give

(16) Substituted cyclopropyl alcohols are known to give rearrangments in acidic medium. See for example: Bernard, A. M.; Floris, C.; Frongia, A.; Piras, P. P. *Synlett* **1998**, 668 and references therein.

(17) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1988.

product **11** as a pale yellow oil (0.45 g, 70%). ^{1}H NMR ($CDCl_3$) δ 5.04 (bs, 1 H), 3.70 (m, 2 H), 3.53 (m, 1 H), 2.90 (bs 2H), 1.64−1.52 (m, 2 H), 1.48 (s, 9 H), 0.91−0.78 (m, 4 H). ^{13}C NMR δ 158.6, 58.7, 57.9, 52.2, 31.8, 28.4, 27.5, 18.2, 7.79. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.28; H, 9.25; N, 5.94.

(2*S*)-1-[(1-Tetrahydropyran-2-yloxy)ethyl]cyclopropanol (15). To a solution of **13** (10 mmol, 1.88 g) and Ti(O*i*-Pr)$_4$ (0.6 mL, 2 mmol) in dry THF (30 mL) at 15° under N_2 atmosphere was added EtMgBr (25 mmol, 7.5 mL) dropwise over 2 h. After an additional 1 h of stirring, the reaction was quenched by addition of a saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated in a vacuum. The residual yellow oil was purified by column chromatography on silica gel (eluent CH_2Cl_2) to afford the cyclopropanol derivative **15** as a pale yellow oil (1.3 g, 70% yield). ^{1}H NMR ($CDCl_3$) δ 5.01−4.95 (m, 1 H) 3.64−3.43 (m, 3 H), 1.40 (m, 6 H), 1.29 (d, J = 6.Hz, 3 H), 0.91−0.74 (m, 4 H). ^{13}C NMR δ 96.68, 80.32, 63.09, 56.68, 31.12, 25.57, 19.86, 17.37, 16.11, 14.33. MS (*m*/*e*) 186 M$^+$. Microanylisis was performed on a sample purified by PTLC (hexane:Et_2O 1: 1). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.48; H 9.27.

3-Methyl-2-oxa-spiro[3.2]hexane 23. Compound **23** was the main product isolated (from 25 to 45% yield) in any attempt to perform a nucleophilic substitution on compound **22**. A representative procedure is following.

To a solution of **22** (0.7 g, 6.1 mmol) and PPh_3 (2.32 g, 9 mmol) in dry THF (30 mL) was added DEAD dropwise (1.4 mL, 9 mmol) under N_2. The mixture was heated at 60 °C for 12 h. The solvent removed in a vacuum and the red residue purified on silica gel column (AcOEt/petroleum ether = 1/1) to give the substitution product **23** as an oil (0.52 g, 40%). ^{1}H NMR ($CDCl_3$) δ 4.50 (m, 1H), 2.20−1.90 (m, 2H), 1.22 (d, J = 7 Hz, 3H), 1.00−0.68 (m, 4 H). ^{13}C NMR δ 65.77, 50.34, 43.23, 22.70, 13.65, 12.50. MS (*m*/*e*) 98 M$^+$. An additional purification on silica gel using pentane as the eluent gave 80 mg of an analytical sample. Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.29.

Methane Sulfonic Acid 1-(2-Methanesulfonyloxypropyl)-cyclopropyl Ester (24). General Procedure. To a solution of diol **7** (1.16 g, 10 mmol) and NEt_3 (19.5 mL, 140 mmol) in dry CH_2Cl_2 (150 mL), under N_2 atmosphere and at room temperature, was added MsCl (2.00 mL, 25 mmol) dropwise. The mixture was stirred for 2 h at room temperature, H_2O was added, and the organic layer was separated. The organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo, to afford **24** (orange oil, 2.10 g, 99% yiel) that was used in the successive step without any purification. ^{1}H NMR ($CDCl_3$) δ 5.11−5.02 (m, 1 H), 2.96 (s, 3 H), 2.94 (s, 3 H), 2.22 (dd, J = 15 and 4 Hz 1 H), 2.00 (dd, J = 15 and 7, 1 H), 1.44 (d, J = 6.Hz, 3 H), 1.38−1.13 (m, 4 H). ^{13}C NMR δ 56.8, 54.7, 47.6, 36.5, 33.7, 23.3, 10.5, 9.9.

Methane Sulfonic Acid 1-[2-(Thymin-1-yl)propyl]cyclopropyl Ester (27). General Procedure. Compound **24** (2.12 g, 10 mmol) was dissolved under N_2 in dry DMF (100 mL). Thymine (2.5 g, 20 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) were added. The reaction mixture was heated at 110 °C for 18 h under vigorous stirring. The solution was filtered and the DMF evaporated under high vacuum to afford a crude solid that was purified on silica gel column (eluent ethyl acetate/petroleum ether = 5/1) to afford product **27** as a dense oil (2.03 g, 70%). ^{1}H NMR ($CDCl_3$) δ 8.01 (bs, 1 H), 6.93 (s, 1 H), 4.80 (m, 1 H), 2.92 (s, 3 H), 2.14 (d, J = 7.Hz, 2 H), 1.85 (d, J = 6.9, 3 H), 1.82 (s, 3 H), 0.83−0.71 (m, 1 H), 0.69−0.58 (m, 2 H), 0.56−0.43 (m, 1 H). ^{13}C NMR δ 164.42, 154.73, 137.93, 109.72, 53.52, 44.68, 42.65, 35.03, 19.37, 16.113, 10.42, 10.31. Anal. Calcd for $C_{12}H_{18}N_2O_5S$: C, 47.67; H, 6.00; N, 9.27. Found: C, 47.75; H, 6.12; N, 9.14.

1-[2-(1-Hydroxycyclopropyl)1-methylethyl]thymine (30). General Procedure for Hydrolysis of the Mesylate. Product **27** (0.4 g, 1.2 mmol) was suspended in an aqueous solution of $LiOH\cdot H_2O$ (51 mg, 1.2 mmol) in H_2O (3.6 mL). The mixture was stirred at 80 °C for 12 h. The solvent was reduced to half volume in vacuo and extracted with AcOEt. The organic layer was separated, dried, over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: a gradient AcOEt → MeOH) to give product **30** as a white solid (0.2 g, 68%). Mp 185−187 °C. ^{1}H NMR (DMSO) δ 8.48 (bs, 1H), 6.99 (s, 1 H), 4.13 (m, 1 H), 3.06 (bs, 1H), 1.92, (s, 3 H), 1.76−1.57 (m, 2 H), 1.37 (d, J = 6.95, 3 H), 1.05−0.87 (m, 4 H). ^{13}C NMR δ 164.42, 154.73, 137.93, 110.76, 53.52, 50.05, 41.63, 19.48, 16.07, 13.52, 12.41. Anal. Calcd For $C_{11}H_{16}N_2O_5$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.77; H, 7.25; N, 12.38.

1-(2-Aminopropyl)cyclopropyl Ester (38). General Procedure. To a solution of dimesylate **24** (0.2 g, 1 mmol) in DMF (10 mL) was added a solution of NaN_3 in DMF. The reaction was stirred at room temperature for 2 h, and then ethyl acetate (10 mL) was added. The organic phase was washed with H_2O, dried over Na_2SO_4, and filtered, and the solvent was evaporated in vacuo. The purification by column chromatography on silica gel (eluent AcOEt) afforded the derivative mesylate as a orange oil (0.16 g, 90%). Product **37** (0.16 g, 0.9 mmol) and triphenylphosphine (0.40 g, 1.5 mmol) were dissolved in dry dioxane (1 mL), and the mixture was stirred at room temperature for 18 h. Ammonium chloride (1 mL of a 1 M solution) was added, and the reaction mixture was stirred for an additional 6 h. The solvents were evaporated, and the residue was purified using flash chromatography (AcOEt) to give the desired amine **38** as a oil (0.11 g, 79%). ^{1}H NMR δ 3.30 (m, 1 H), 2.69 (bs, 3 H), 2.16 (m, 2 H), 1.40 (d, J = 7, 3 H), 1.01−0.90 (m, 4 H). ^{13}C NMR δ 57.0, 49.8, 39.9, 26.9, 14.0, 13.7. Microanalytical data of the corresponding *p*-nitrobenzamide.[18] Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.18; H, 6.12, N, 10.63.

Methane Sulfonic Acid 1-(1-Hydroxyethyl)cyclopropyl Ester (41). To a solution of **15** (0.36 g, 2 mmol) and NEt_3 (1.95 mL, 14 mmol) in dry CH_2Cl_2 (15 mL) was added MsCl (0.2 mL, 25 mmol) dropwise under N_2 atmosphere and at room temperature. After 2 h, the reaction mixture was washed with H_2O (3 × 100 mL), dried over Na_2SO_4, filtered, and evaporated in a vacuum, to afford an orange oil in quantitative yield that was used in the successive step without any purification. The obtained mesylate (0.52 g, 2 mmol) was dissolved in MeOH (10 mL), and a catalytic amount of pTsOH was added. The mixture was stirred at room temperature for 18 h, and then $NaHCO_3$ was added. The solution was filtered on Celite, the solvent was distilled, and the crude oil was purified on a silica gel column (AcOEt/CH_2Cl_2 = 1/1) to give the product as a yellow oil (0.29 g, 80%). ^{1}H NMR ($CDCl_3$) δ 4.85 (d, J = 6.7, 1 H), 3.01 (s, 3 H), 1.54−1.47 (m, 1 H), 1.23 (d, J = 6.13, 3 H), 1.22−1.17 (m, 2 H), 0.99−0.91 (m, 1 H), 0.89−0.83 (m, 1 H). ^{13}C NMR δ 70.21, 39.67, 20.96, 18.85, 10.76, 9.42. Anal. Calcd For $C_6H_{12}O_4S$: C, 39.99; H, 6.71. Found: C, 39.87; H, 6.75;.

Methane Sulfonic Acid 1-[1-(Thymin-1-yl)ethyl]cyclopropyl Ester (42). To a solution of **41** (1 g, 6 mmol) and PPh_3 (2.32 g, 9 mmol) in dry THF (30 mL) was added thymine portionwise (0.75 g, 6 mmol) followed by DEAD (1.4 mL, 9 mmol) under N_2. The mixture was heated at 60 °C for 12 h. The solvent was removed in vacuo and the red residue purified on silica gel column (AcOEt/hexane = 1/1) to give the substitution product **42** as a waxy material (0.52 g, 40%). ^{1} H NMR ($CDCl_3$) δ 7.61 (bs, 1H), 7.10 (s, 1H), 4.54 (m, 1H), 3.02 (s, 3H), 2.31 (s, 3H), 1.42 (d, J = 8 Hz, 3H), 0.85−0.65 (m, 4H). ^{13}C NMR δ 164.4, 155.8, 137.9 109.9, 61.8, 55.5, 34.8, 19.9, 15.3, 10.7. Anal. Calcd For $C_{11}H_{16}N_2O_5S$: C, 45.82; H, 5.59; N, 9.72. Found: C, 45.78; H, 5.65; N, 9.76.

MTPA Ester 44. The product was prepared directly in the NMR tube following the standard procedure. ^{19}F NMR (TFA internal standard) δ 5.03 (91%), 4.93 (9%).

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Supporting Information Available: Spectral data of compounds **8**−**10**, **12**, **16**, **25**, **26**, **28**, **29**, **31**−**36**, **40**, and **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Prepared form *p*-nitrobenzoyl chloride following the classical Schotten−Baumann reaction conditions: Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific &Technical: London, 1989; p 1273.

(19) Ohtani, I.; Kusuni, T. P.; Koshman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.