46. Carbocyclic Analogs of Nucleosides

Part 4[1])

Preparation of Enantiomerically Pure Analogs of Purine Nucleosides for the Synthesis of Sulfone-Linked Oligonucleotide Analogs

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Cyclopentane derivatives bearing a 3-(hydroxymethyl) group, a 4-(2-hydroxyethyl) functionality, and a nucleoside base are carbocyclic variants of nucleoside analogs previously described as building blocks for the preparation of oligonucleotide analogs having dimethylene sulfone (= methanosulfonylmethano) linking groups replacing the phosphodiester linking units found in natural oligonucleotides. These carbocyclic nucleoside analogs (*e.g.* **17** and **20**) are stable to both acid-catalyzed depurination and base-catalyzed hydrolysis, in contrast with most non-ionic analogs of oligonucleotides. Furthermore, they can be prepared with complete control over the stereochemistry at the 'anomeric' center. A procedure is given for preparing these purine-nucleoside analogs *via* the construction of an enantiomerically pure carbocyclic skeleton (*Schemes 1–3*), followed by a *Mitsunobu*-type reaction to introduce the purine-base derivatives (*Scheme 4*). Furthermore, preliminary results for the coupling of these analogs to yield nucleoside dimers (*e.g.* **26**) are also reported (*Scheme 5*).

Introduction. – The interaction between complementary oligonucleotide strands is one of the most noteworthy examples of molecular recognition known to chemistry. This interaction is especially remarkable in that, from a chemical perspective, nucleic acids appear to be poorly designed for the purpose. The recognizing moiety is flexible, implying that complex formation must be accompanied by a large loss of conformational entropy. Specificity of complex formation is determined by H-bonding, a fact which is remarkable in an aqueous medium where H-bonds to solvent are readily available. Nevertheless, the recognition phenomenon is highly specific, can extend over great lengths, and is the basis for the storage and transmission of genetic information of all living systems presently known.

We and others are involved in long-term research programs seeking to systematically modify oligonucleotides to better understand this recognition phenomenon [2] [3]. One aspect of these works involves preparing non-ionic analogs of oligonucleotides. These attracted interest in the last decade as molecules with the potential of being stable to enzymatic and biological degradation, passing across biological barriers, and binding to complementary oligonucleotides with sequence specificity, thereby blocking their biolog-

[1]) Part 3: [1].

ical activity. The third quality, the basis of 'antisense' control of the expression of specific mRNA's, is a simple extension of *Watson-Crick* base-pairing rules [4] applied to messenger RNA molecules [5–9]. The success of antisense strategies depends on the conservation of the molecular recognition properties displayed by natural oligonucleotides in their structural variants.

One characteristic of all oligonucleotides and their analogs based on a furanose ring system is instability under acidic conditions. The primary reaction in acid is the loss of the purine base [10] [11]. Depurination is a significant problem in the laboratory synthesis of oligonucleotides, and presumably is a route for the degradation of oligonucleotides under natural conditions as well [11] [12].

Under alkaline conditions, natural DNA is stable. Analogs of DNA, in particular non-ionic analogs based on phosphate-type linkers, generally are not. *E.g.*, phosphate triesters are *ca.* 5 log units more reactive towards attack by OH^- than is the corresponding phosphate diester monoanion. The combination of acid and alkaline instability creates problems in the synthesis of non-ionic oligonucleotide analogs, making selection of protecting groups particularly difficult. These problems were best illustrated by difficulties recently encountered in research directed towards the preparation of methyl phosphate triester analogs of DNA as antiviral agents [13]. Similar, although much less severe, sensitivity to alkaline hydrolysis is displayed by oligonucleotide analogs joined by methyl phosphonate [14] and analogous linking groups.

Yet another problem arises in the synthesis of analogs of 2′-deoxynucleosides. In ribonucleoside analogs, substituents at the 2′-position can assist in the control of stereochemistry at the anomeric center. Base introduction in, *e.g.*, 2-*O*-acetyl derivatives of D-ribose invariably yield the β-D-anomer. Similar control of stereochemistry is not possible in the preparation of 2′-deoxyriboside analogs. In many syntheses of 2′-deoxynucleoside derivatives, a mixture of anomers is obtained that must be separated.

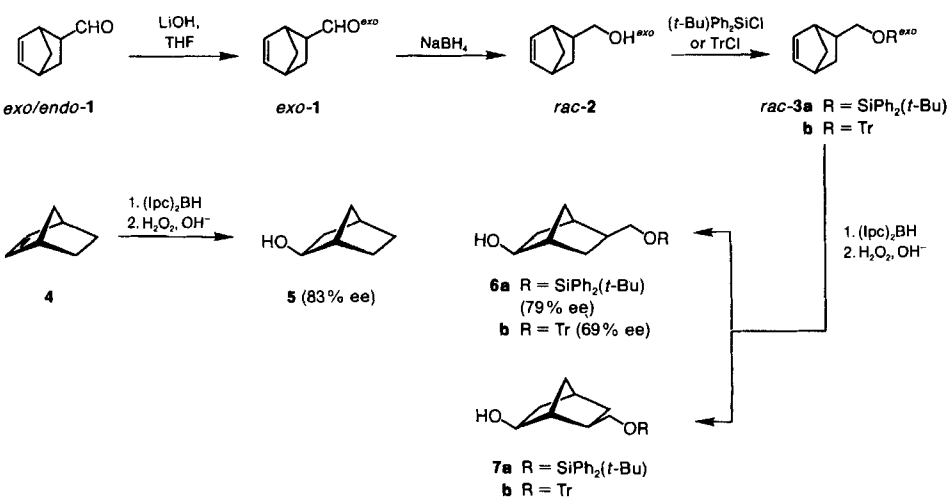
Recently, we suggested that dimethylene-sulfone units can replace phosphate diesters in antisense oligonucleotide analogs [15] [16]. Such structures have advantages over many other non-ionic oligonucleotide analogs that were proposed. Unlike non-ionic analogs based on a P-linkage, the linking unit in an oligosulfone is not stereogenic and thus allows the preparation of analogs free of diastereoisomeric mixtures. The lipophilicity of sulfone-containing oligonucleotide analogs should assist their membrane permeability. Finally, sulfones are stable to hydrolysis, both enzymatic and chemical under alkaline conditions. Syntheses for these molecules were recently reported [17].

Although devoid of functional groups that are unstable under alkaline conditions, sulfone-linked oligonucleotide analogs still incorporate the N,O-acetal functionality found in natural oligonucleotides and, therefore, are sensitive to acidic conditions. Furthermore, standard routes for preparing 2′-deoxy variants of building blocks needed for the synthesis of sulfone-linked oligonucleotide analogs either yield a mixture of anomers, or must be prepared *via* the corresponding ribo derivatives followed by deoxygenation [18]. One structural modification that avoids both problems involves the replacement of the 'furanose' ring O-atom with a CH_2 group in these building blocks (*e.g.* **17** and **20**, *Scheme 4*). Such carbocyclic sugar analogs contain no N,O-acetal functionality and should be rather stable under acidic conditions. Moreover, as derivatives of cyclopentylamine, it should be possible to prepare these nucleoside analogs with full diastereochemical control.

Recently, carbocyclic nucleotides containing natural phosphodiester bridges as backbone were prepared. It was reported that these molecules are at least 5 times more stable toward enzymatic degradation and that oligonucleotide analogs built from these bind more strongly to natural single-stranded DNA than does DNA itself [19] [20]. These findings prompt us to report here the preparation of carbocyclic 3′,5′-bis(methylene)-substituted analogs of 2′-deoxynucleosides, building blocks for oligonucleotide analogs where both the phosphodiester bridges are replaced by dimethylene sulfone groups, and the furanose ring O-atom is replaced by a CH_2 group. Preliminary work for the coupling of these molecules is also reported. In the synthesis, a novel method for alkylating nucleoside bases using *Mitsunobu* conditions was developed and applied [21], as was a specially protected derivative of guanosine [22].

Results. – *Enantiomerically Enriched Precursors.* The cyclopentane skeletons **14a** and **14b** required for the introduction of purine bases under *Mitsunobu* conditions were constructed from commercially available racemic norbornenecarbaldehyde *exo/endo*-**1** (*Scheme 1*). Two routes were developed; they differ in the strategy used to protect

Scheme 1

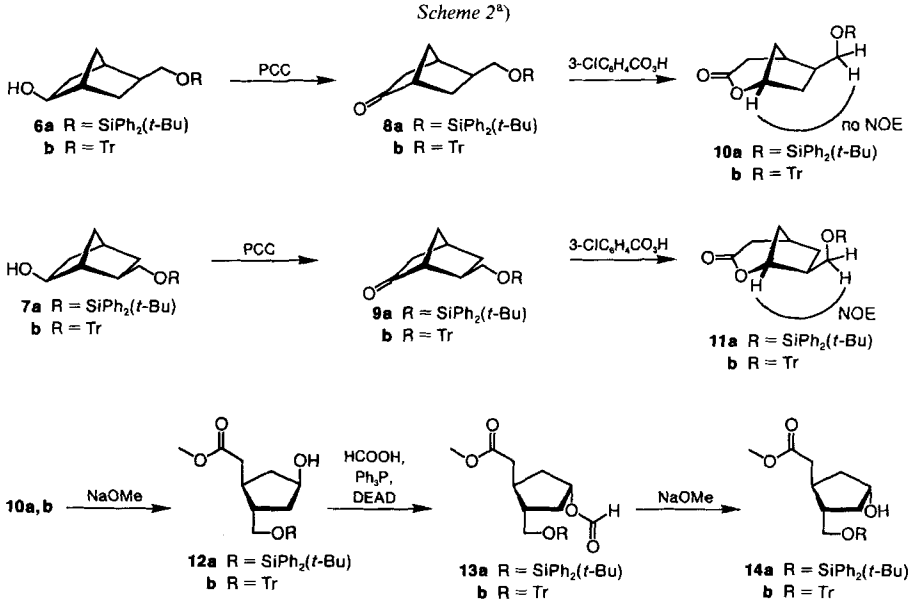


functional groups during the synthesis. The primary OH function in *rac*-**2** [1], which becomes the side chain on C(3′) in the final nucleosides, was protected either as a silyl ether (89% yield) using (*tert*-butyl)diphenylsilyl chloride ((*t*-Bu)Ph_2SiCl) [23] or as a trityl ether (quant. yield) using a modified procedure from *Reddy et al.* [24] [25]. Both protecting groups proved to be preferable to the simple acetyl protecting group for the separation of regioisomers **6a** and **7a** or **6b** and **7b** obtained from the subsequent hydroboration of *rac*-**3a** or *rac*-**3b**. Substantial enantiomeric control could be achieved in this synthesis by stereoselective hydroboration with di(isopinocamphenyl)borane ($(Ipc)_2BH$), developed by *Brown* and coworkers and applied to the synthesis of trinor-

bornanol (**5**) from trinorbornene (**4**) to yield product with an 83% enantiomeric excess [26] (*Scheme 1*). Applying $(Ipc)_2BH$, prepared from (+)-(1*R*)-α-pinene, to the silyl derivative *rac*-**3a** or the trityl derivative *rac*-**3b** yielded isomers **6a** or **6b**, respectively, which have skeletons appropriate as precursors for carbocyclic nucleosides with chirality of the same sense as in natural nucleosides. Assuming that the selectivity of the hydroboration was essentially independent of the substituent on the far side of the trinorbornene skeleton, the products were two sets of regioisomers, either **6a** (33%) and **7a** (33%) in the silyl series, or **6b** (50%) and **7b** (45%) in the trityl series. In both series, the enantiomeric excesses of the desired regioisomers **6a** (79% ee) and **6b** (69% ee) were almost as high as for trinorbornanol (83% ee). Thus, hydroboration of *rac*-**3a** or *rac*-**3b** and separation of the regioisomers **6a** and **7a** or **6b** and **7b** corresponded to an overall resolution of *rac*-**3a** or *rac*-**3b**.

After oxidation of **6** and **7** with pyridinium chlorochromate (PCC) [27] [28] to **8a** (87%) and **9a** (80%) or **8b** (quant.) and **9b** (93%), respectively, and *Bayer-Villiger* reaction with 3-chloroperbenzoic acid [29] to **10a** (95%) and **11a** (quant.) or **10b** (93%) and **11b** (78%), respectively, the configurations of **6a** and **7a** could be assigned by correlation to the structures of **10a** and **11a**, respectively; those of **6b** and **7b** were

Scheme 2[a])



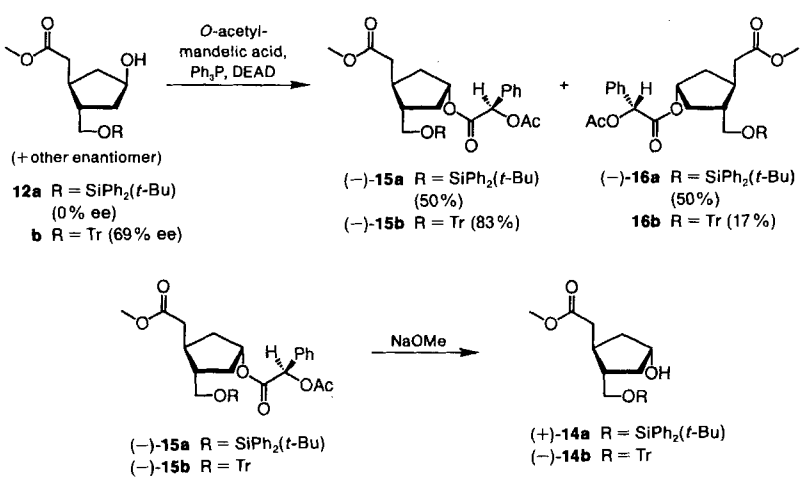
[a]) All compounds are enantiomerically enriched.

correlated to **10b** and **11b**, respectively (*Scheme 2*). In **10a** as well as **10b**, a nuclear *Overhauser* effect (NOE) between the bridgehead H-atom adjacent to the lactone (H–C(1)) and the methylene group protons in the side chain (CH_2OR) was not observed. In contrast, **11a** and **11b** showed strong NOE's between these H-atoms.

Opening of the lactone ring in **10a** or **10b** yielded hydroxy-esters **12a** (96%) or **12b** (93%), respectively, containing OH functionalities on the β-side when viewed as ribose analogs (*Scheme 2*). The configurations at the alcohol centers were, therefore, inverted using formic acid under *Mitsunobu* conditions [30] to yield diastereoisomers **14a** (94% rel. to **12a**) and **14b** (77% rel. to **12b**), where the OH groups are amenable to S_N2 displacement by bases to yield nucleoside analogs with 'β'-configuration.

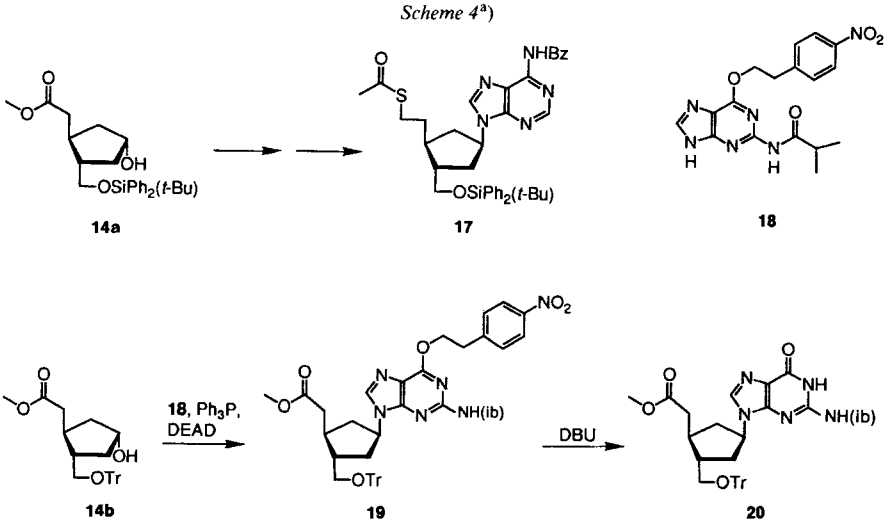
Enantiomerically Pure Precursors. Remarkably, crystallization at several steps en route to nucleoside precursors **14a** and **14b** failed to increase the enantiomeric excesses. However, (+)-**14a** or (−)-**14b** with enantiomeric excesses approaching 100% could be obtained by chromatographic separation of the (*R*)-*O*-acetylmandelic-acid derivatives (−)-**15a** and (−)-**15b**, prepared from **12a** and **12b**, respectively, with inversion at the alcohol center under *Mitsunobu* conditions using (−)-(*R*)-*O*-acetylmandelic acid (*Scheme 3*). This procedure has the virtue of solving two stereochemical problems simultaneously without increasing the number of steps in the synthesis. Surprisingly, isomers (−)-**15a** and (−)-**16a** of the silyl series proved to be much easier to separate by chromatography than the corresponding isomers (−)-**15b** and **16b** of the trityl series.

Scheme 3



Nucleoside-Base Introduction. A set of *Mitsunobu* conditions was developed that proved to be useful for introducing a range of purine and pyrimidine derivatives into carbocyclic skeletons [21] [31]. The adenosine building block **17** was synthesized as previously reported using these procedures [1]. The guanosine building-block precursor **20** was formed *via* intermediate **19** (71%) applying conditions analogous to those described for the 2′,3′-dideoxy variants [32] followed by deprotection (95%) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [33] (*Scheme 4*). The yield of the S_N2 displacement of the secondary OH function in **14b** with N^2-isobutyryl-O^6-[2-(4-nitrophenyl)ethyl]guanine (**18**) [22] was not affected by the additional side chain on C(3′), not present in the corresponding 2′,3′-dideoxyguanosine analog. For 6-chloropurine as well as **18**, undesired alkylation at N^7 of the purine ring was not observed.

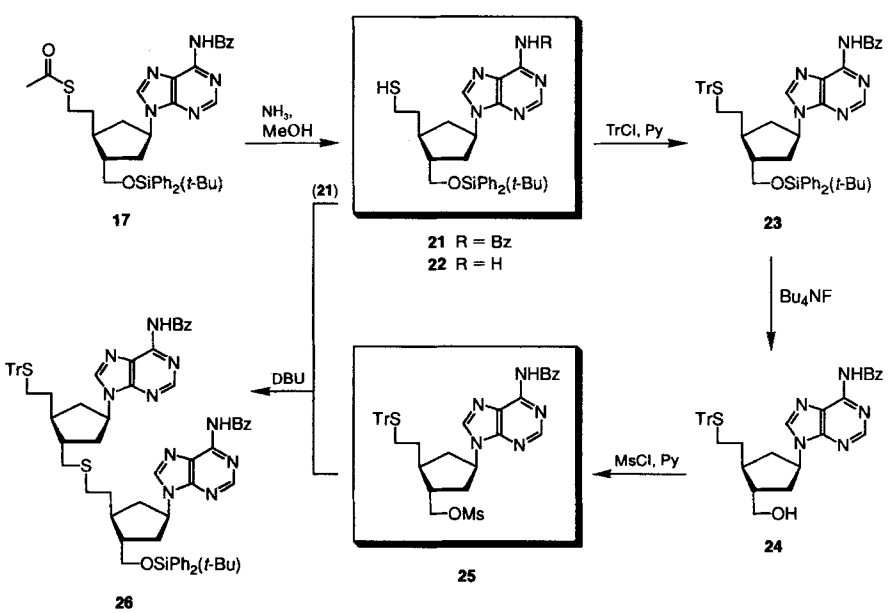
Scheme 4[a])



[a]) All compounds are enantiomerically enriched.

Further Transformations. Removing the acetyl group on the longer side chain of **17** with NH_3 in MeOH at 0° yielded the first building block **21** (69%), required for the synthesis of a dimer (*Scheme 5*). Prolonged use of NH_3 in MeOH at room temperature

Scheme 5[a])



[a]) All compounds are enantiomerically enriched.

resulted in complete loss of the acetyl as well as the benzoyl protecting groups, yielding **22** (89%) instead of **21**. The second building block **25** was obtained by blocking the free thiol in **21** with a trityl group (→**23** (80%)), removal of the silyl group (→**24** (91%)), and activation of the OH function with mesyl chloride to give **25** (quant.). A sample of the dimer **26**, contaminated with a disulfide derived from **21** (produced by traces of O_2 present during coupling), could be obtained by reacting the two building blocks in the presence of DBU (*Scheme 5*).

Discussion. – In this work, enantiomerically pure building-block precursors were produced *via* a stereoselective hydroboration followed by an inversion of configuration at an alcohol center using a chiral acid. This is an efficient and elegant way to produce the configuration desired for carbocyclic nucleoside analogs without increasing the total number of steps in the synthesis. As *O*-acetylmandelic acid is inexpensive, the central issue becomes the cost of the chiral auxiliary used in the asymmetric hydroboration. The silyl route seems to be more favorable than the trityl route, because the enantiomeric excess after the hydroboration is higher and separation of the diastereoisomers after the substitution with *O*-acetylmandelic acid is easier.

The *Mitsunobu* reaction seems to be generally applicable for the introduction of nucleoside bases onto C-skeletons. Even in cyclopentane derivatives that bear a side chain at the C-atom next to the OH function (*e.g.* in 3-substituted methyl 4-hydroxycyclopentaneacetates)[2]), the yield of the substitution of the OH function with nucleoside-base derivatives depended only moderately on the structure of the skeleton. The rigorous control of stereochemistry, the absence of marked influence of the structure of the C-skeleton on the yield of the reaction, and the diversity of heterocyclic functions that work in this procedure all suggest that it will be applicable to many problems similar to the one reported in this series in the future.

In forming analogs of dinucleotides, analogs of nucleosides are used as building blocks in an S_N2 reaction, where one building block contributes a thiolate anion as a nucleophile, and the other contributes a primary mesylate as an electrophile. In principle, either component could contribute either functionality. We found in this work and in further experiments with furanose building blocks [34] that *intermolecular* coupling proceeds better, however, if the 5′-center (assigned by analogy with ribose derivatives) bears the mesylate, while the 3′-center bears the thiolate. The intermolecular coupling is less efficient, if the 3′-center bears the mesylate and the 5′-center the thiolate. This is not unexpected on simple stereoelectronic grounds, of course. Displacement of a leaving group on a C-atom adjacent to a branched center is well known in physical organic chemistry; perhaps the most extreme example is the slow S_N2 displacement seen at neopentyl centers. As the concentration of building blocks under coupling conditions is typically rather low, and as the thiolate can undergo a competing oxidation to yield disulfide in the presence of traces of O_2, the yields of dinucleotide analogs are markedly different in the two coupling modes. An interesting possibility derived from *Part 3* of this series [1] is that *intramolecular* S_N2 reactions appear to proceed best, if the 3′-center bears the mesylate, and the 5′-center bears the thiolate.

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[2]) For full experimental details of this series, in which the skeletons were derived from **11a** or **11b**, see [31].

Efficient syntheses of building blocks, as described in this paper, are necessary for the preparation of analogs of oligonucleotides having uncharged, isosteric, and isoelectronic CH_2–S–CH_2, CH_2–SO–CH_2, and CH_2–SO_2–CH_2 bridges replacing the negatively charched O–PO_2–O groups in natural oligonucleotides. Progress in this area will be reported separately.

Experimental Part

General. See [32]. The concentration of active hydrogen in commercially available or freshly prepared BH_3-THF was determined prior to the stereoselective hydroboration steps by measuring the volume of H_2 evolved upon treating an aliquot with dil. AcOH [35]. Prep. TLC: *Merck* silica gel *60F254* precoated PSC plates, $d = 2$ mm. Optical rotations $[\alpha]_D$: *Perkin-Elmer-241* polarimeter; $d = 10$ cm, c in g/100 ml.

5-exo-{*[(*tert-*Butyl)diphenylsilyloxy]methyl*}*bicyclo[2.2.1]hept-2-ene* ((±)-**3a**). A soln. of (±)-**2** (28.5 g, 230 mmol; freshly distilled at 75°/10 Torr) [1] and imidazole (31.3 g, 460 mmol) in CH_2Cl_2 (220 ml) was treated at −10° for 1 h with (*t*-Bu)Ph_2SiCl (76.6 ml, 300 mmol). The mixture was stirred at r.t. for 1 h, treated with H_2O (12 ml), and extracted twice with CH_2Cl_2 (500 ml). The org. extracts were washed with brine, dried ($MgSO_4$), and evaporated. FC (silica gel (1000 g), pentane/Et_2O 99:1) yielded (±)-**3a** (73.8 g, 89%). Viscous oil. IR (CCl_4): 3075, 2965, 2935, 2900, 2860, 1470, 1460, 1430, 1190, 1110, 1095, 1070, 1005, 865, 705, 615. ^{1}H-NMR ($CDCl_3$): 1.06 (*s*, *t*-Bu); 1.12–1.28 (*m*, 4 H); 1.63–1.73 (*m*, 1 H); 2.75 (br. *s*, 1 bridgehead H); 2.84 (br. *s*, 1 bridgehead H); 2.53 (*dd*, $J = 9.1$, 10.1, 1 H, CH_2O); 3.73 (*dd*, $J = 6.1$, 10.1, 1 H, CH_2O); 6.04 (*dd*, $J = 2.8$, 5.6, 1 olef. H); 6.11 (*dd*, $J = 3.0$, 5.6, 1 olef. H); 7.34–7.41 (*m*, 6 arom. H); 7.65–7.69 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 19.31 (*s*, Me_3CSi); 26.90 (*q*, Me_3CSi); 29.17 (*t*); 41.52 (*d*); 43.38 (*d*); 44.80 (*t*); 68.13 (*t*, CH_2O); 127.60 (*d*, CH, Ph_2Si); 129.52 (*d*, CH, Ph_2Si); 134.14 (*s*, C, Ph_2Si); 135.63 (*d*, CH, Ph_2Si); 136.74 (*d*, *C*H=*C*H, overlapping). MS: 361 (< 1, $[M - 1]^+$), 306 (13), 305 (47), 239 (38), 227 (25), 200 (18), *199* (100), 197 (17), 183 (28), 181 (14), 161 (49), 135 (12), 105 (18), 91 (12), 79 (16), 77 (22), 67 (21), 53 (10), 41 (22). Anal. calc. for $C_{24}H_{30}OSi$ (362.6): C 79.50, H 8.34; found: C 79.48, H 8.35.

*(1*R*,2*S*,4*R*,5*S*)-5-{[(*tert-*Butyl)diphenylsilyloxy]methyl*}*bicyclo[2.2.1]heptan-2-ol* (**6a**) *and (1*R*,2*S*,4*R*,6*R*)-6-{[(*tert-*Butyl)diphenylsilyloxy]methyl*}*bicyclo[2.2.1]heptan-2-ol* (**7a**). A soln. of (+)-(1*R*)-α-pinene (49 ml, 310 mmol; $[\alpha]_D^{22°} = +47.1$, > 91% ee; freshly distilled from Na and benzophenone) was treated at −35° with 0.82M BH_3-THF (182 ml, 150 mmol). The mixture was stirred for 24 h at 0° and 24 h at −10°. The precipitate was allowed to settle and the supernatant (120 ml) removed by suction with a needle. The precipitate was cooled to −38°, and a soln. of (±)-**3a** (36 g, 100 mmol; dried for 48 h under high vacuum) in THF (15 ml) was added. The mixture was stirred for 14 h at −25°, 24 h at −20°, and 24 h at −10°, over which time the suspension became a clear colorless soln. The mixture was allowed to warm to 0°, treated for 30 min with 3N aq. NaOH (60 ml), and then for 30 min with 30% aq. H_2O_2 soln. (60 ml). The mixture was stirred at r.t. for 1 h, $NaHSO_3$ (20 g) was added, and the mixture was extracted with Et_2O. The org. extract was washed with brine, dried ($MgSO_4$), and evaporated. The side-product α-pinanol was removed by distillation at 130°/0.7 Torr and the residue adsorbed on silica gel (70 g). FC (silica gel (2000 g), hexane/AcOEt 75:25) yielded enantiomerically enriched **6a** (12.4 g, 33%) and **7a** (12.3 g, 33%), as well as recovered racemic starting material (±)-**3a** (8.2 g, 23%).

Data of **6a**: Colorless foam. TLC (silica gel, hexane/AcOEt 75:25): R_f 0.24. 79% ee (measured by reaction with (+)-(*S*)-*Mosher*'s acid chloride [36] ($[\alpha]_D^{20°} = +135.5$ ($c = 5.2$, CCl_4); > 99% ee) in pyridine to a mixture of diastereoisomers (ratio from the ^{19}F-NMR integrals, 89:11). IR (CCl_4): 3600, 3070, 2960, 2860, 1590, 1470, 1430, 1360, 1260, 1245, 1110, 1080, 1030, 1005, 925, 700. ^{1}H-NMR ($CDCl_3$): 0.92 (*dt*, $J = 12.8$, 4.6, 1 H); 1.05 (*s*, *t*-Bu); 1.10–1.18 (*m*, 2 H); 1.29–1.36 (*m*, 1 H); 1.38 (*s*, OH); 1.40–1.45 (*m*, 1 H); 1.53–1.63 (*m*, 1 H); 1.70 (*ddd*, $J = 2.4$, 6.8, 13.2, 1 H); 2.06 (br. *d*, $J = 4.5$, 1 bridgehead H); 2.30 (br. *d*, $J = 4.4$, 1 bridgehead H); 3.36 (*d*, $J = 2.8$, 1 H, CH_2O); 3.39 (*d*, $J = 1.2$, 1 H, CH_2O); 3.75–3.78 (*m*, H–C(2)); 7.34–7.44 (*m*, 6 arom. H); 7.64–7.68 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 19.28 (*s*, Me_3CSi); 26.90 (*q*, Me_3CSi); 28.42 (*t*); 30.98 (*t*); 37.36 (*d*); 42.67 (*t*); 43.28 (*d*); 44.38 (*d*); 67.17 (*t*, CH_2O); 74.73 (*d*, C(2)); 127.61 (*d*, CH, Ph_2Si); 129.55 (*d*, CH, Ph_2Si); 134.05 (*s*, C, Ph_2Si); 135.61 (*d*, CH, Ph_2Si). MS: 380 (< 1, M^+), 324 (22), 323 (82), 200 (19), *199* (100), 197 (11), 183 (16), 181 (13), 135 (12), 107 (10), 105 (11), 79 (29), 77 (15), 41 (13).

Data of **7a**: Colorless foam. TLC (silica gel, hexane/AcOEt 75:25): R_f 0.34. IR (CCl_4): 3620, 3075, 2960, 2860, 1470, 1430, 1385, 1360, 1260, 1225, 1115, 1085, 1005, 940, 915, 860, 700. ^{1}H-NMR ($CDCl_3$): 0.84–0.92 (*m*, 1 H); 1.05 (*s*, *t*-Bu); 1.10–1.18 (*m*, 2 H); 1.26–1.32 (*m*, 1 H); 1.39 (*s*, OH); 1.43–1.48 (*m*, 1 H); 1.51–1.58 (*m*, 1 H); 1.64 (*ddd*, $J = 2.3$, 6.9, 13.2, 1 H); 2.19–2.22 (*m*, 2 bridgehead H); 3.37–3.48 (*m*, CH_2O); 3.78–3.97 (*m*, H–C(2));

7.35–7.45 (*m*, 6 arom. H); 7.65–7.68 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 19.38 (*s*, Me_3CSi); 26.96 (*q*,Me_3CSi); 31.51 (*t*); 32.41 (*t*); 35.30 (*d*); 39.99 (*d*); 41.96 (*t*); 46.69 (*d*); 66.87 (*t*, CH_2O); 74.99 (*d*, C(2)); 127.59 (*d*, CH, Ph_2Si); 129.52 (*d*, CH, Ph_2Si); 134.11 (*s*, C, Ph_2Si); 135.61 (*d*, CH, Ph_2Si). MS: 380 (< 1, M^+), 324 (17), 323 (62), 245 (26), 200 (18), *199* (100), 197 (12), 183 (15), 181 (14), 139 (14), 135 (16), 107 (15), 105 (15), 91 (11), 85 (12), 83 (19), 79 (32), 77 (18), 67 (11), 57 (11), 41 (17).

*(1R,4R,5S)-5-{[(*tert*-Butyl)diphenylsilyloxy]methyl}bicyclo[2.2.1]heptan-2-one* (**8a**). A soln. of **6a** (12.4 g, 33 mmol) in CH_2Cl_2 (250 ml) was added at 0° within 30 min to a strongly stirred suspension of pyridinium chlorochromate (14.0 g, 65 mmol) and *Celite* (18 g) in CH_2Cl_2 (250 ml). The mixture was stirred at r.t. for 4 h, concentrated to $^1/_3$ of the original volume and filtered through silica gel (180 g). Evaporation yielded **8a** (10.7 g, 87%). Viscous oil. IR (CCl_4): 3075, 2960, 2930, 2895, 2830, 1750, 1470, 1460, 1430, 1410, 1390, 1360, 1185, 1145, 1110, 1090, 1005, 970, 935, 900. ^{1}H-NMR ($CDCl_3$): 1.06 (*s*, *t*-Bu); 1.29 (*dt*, *J* = 13.3, 4.8, 1 H); 1.57–1.64 (*m*, 3 H); 1.79–1.86 (*m*, 1 H); 1.90–1.97 (*m*, 1 H); 2.10 (*dd*, *J* = 4.6, 17.7, 1 H); 2.51 (br. *d*, *J* = 4.4, 1 bridgehead H); 2.66 (br. *d*, *J* = 3.6, 1 bridgehead H); 3.48 (*dd*, *J* = 8.6, 10.3, 1 H, CH_2O); 3.56 (*dd*, *J* = 6.1, 10.3, 1 H, CH_2O); 7.35–7.46 (*m*, 6 arom. H); 7.64–7.68 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 19.26 (*s*, Me_3CSi); 26.88 (*q*, Me_3CSi); 27.71 (*t*); 34.44 (*t*); 37.24 (*d*); 42.65 (*d*); 45.55 (*t*); 49.86 (*d*); 66.71 (*t*, CH_2O); 127.70 (*d*, CH, Ph_2Si); 129.71 (*d*, CH, Ph_2Si); 133.67 (*s*, C, Ph_2Si); 135.59 (*d*, CH, Ph_2Si); 218.13 (*s*, CO). MS: 378 (< 1, M^+), 322 (27), *321* (100), 200 (12), 199 (66), 183 (21), 181 (10), 77 (10), 41 (10).

*(1R,4R,6R)-6-{[(*tert*-Butyl)diphenylsilyloxy]methyl}bicyclo[2.2.1]heptan-2-one* (**9a**). As described for **8a**, with **7a** (300 mg, 0.8 mmol) in CH_2Cl_2 (6 ml), pyridinium chlorochromate (345 mg, 1.6 mmol), and *Celite* (450 mg) in CH_2Cl_2 (6 ml). Workup yielded **9a** (240 mg, 80%). Viscous oil. IR (CCl_4): 3070, 2960, 2930, 2895, 2860, 1755, 1470, 1430, 1410, 1390, 1365, 1300, 1265, 1210, 1165, 1150, 1110, 1080, 1020, 1005, 940, 865. ^{1}H-NMR ($CDCl_3$): 1.05 (*s*, *t*-Bu); 1.28–1.37 (*m*, 1 H); 1.52–1.65 (*m*, 3 H); 1.85 (*dd*, *J* = 3.9, 17.8, 1 H); 2.01–2.12 (*m*, 2 H); 2.62 (br. *s*, 1 bridgehead H); 2.66 (br. *s*, 1 bridgehead H); 3.46–3.57 (*m*, CH_2O); 7.35–7.45 (*m*, 6 arom. H); 7.63–7.66 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 19.31 (*s*, Me_3CSi); 26.95 (*q*, Me_3CSi); 31.77 (*t*); 34.44 (*t*); 35.39 (*d*); 38.86 (*d*); 44.84 (*t*); 52.34 (*d*); 66.06 (*t*, CH_2O); 127.70 (*d*, CH, Ph_2Si); 129.69 (*d*, CH, Ph_2Si); 133.71 (*s*, C, Ph_2Si); 135.61 (*d*, CH, Ph_2Si); 217.10 (*s*, CO). MS: 378 (< 1, M^+), 322 (37), *321* (100), 243 (15), 200 (13), 199 (76), 197 (12), 183 (25), 181 (18), 139 (16), 135 (14), 105 (24), 91 (13), 79 (38), 77 (25), 67 (13), 57 (14), 45 (11), 41 (30).

*(1R,5R,6S)-6-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-2-oxabicyclo[3.2.1]octan-3-one* (**10a**). A suspension of **8a** (5.35 g, 14 mmol) and $NaHCO_3$ (1.78 g, 21 mmol) in CH_2Cl_2 (30 ml) was treated portionwise with 3-chloroperbenzoic acid (80%; 3.96 g, 18 mmol) at 0°. The mixture was stirred in the dark for 18 h at 4°, cooled to 0°, diluted with CH_2Cl_2 (40 ml), and slowly treated with sat. $NaHCO_3$ soln. (50 ml) and 10% aq. $NaHSO_3$ soln. (30 ml). The mixture was allowed to warm to r.t., extracted twice with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and evaporated. FC (silica gel, pentane/Et_2O 1:1) yielded **10a** (5.30 g, 95%). Colorless foam. IR (CCl_4): 3070, 2960, 2930, 2895, 2830, 1745, 1470, 1430, 1375, 1230, 1195, 1170, 1115, 1080, 1055, 1010, 990, 955, 940, 905, 890. ^{1}H-NMR ($CDCl_3$): 1.05 (*s*, *t*-Bu); 1.53 (*dt*, *J* = 13.7, 4.7, 1 H); 1.73–1.79 (*m*, 1 H); 1.85 (br. *d*, *J* = 13.0, 1 H); 2.17–2.31 (*m*, 2 H); 2.46–2.45 (*m*, 2 H); 2.74 (*dd*, *J* = 5.1, 18.6, 1 H); 3.43 (*dd*, *J* = 7.3, 10.2, 1 H, CH_2O); 3.55 (*dd*, *J* = 5.3, 10.2, 1 H, CH_2O); 4.82–4.83 (*m*, H–C(1)); 7.36–7.47 (*m*, 6 arom. H); 7.61–7.64 (*m*, 4 arom. H); NOE: irrad. at 4.82–4.83 (H–C(1))→no increase in intensity at 3.43, 3.55 (CH_2O). ^{13}C-NMR ($CDCl_3$): 19.25 (*s*, Me_3CSi); 26.87 (*q*, Me_3CSi); 33.76 (*t*); 34.25 (*d*); 36.06 (*t*); 41.27 (*t*); 44.80 (*d*); 66.43 (*t*, CH_2O); 81.41 (*d*, C(1)); 127.78 (*d*, CH, Ph_2Si); 129.84 (*d*, CH, Ph_2Si); 133.39 (*s*, C, Ph_2Si); 135.55 (*d*, CH, Ph_2Si); 170.37 (*s*, CO). MS: 394 (< 1, M^+), 338 (19), 337 (68), 308 (10), 307 (39), 263 (11), 259 (12), 215 (38), 200 (18), *199* (100), 197 (15), 183 (33), 181 (20), 139 (10), 135 (13), 105 (15), 77 (22), 45 (10), 41 (23). Anal. calc. for $C_{24}H_{30}O_3Si$ (394.6): C 73.05, H 7.66; found: C 73.12, H 7.72.

*(1R,5R,7S)-7-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-2-oxabicyclo[3.2.1]octan-3-one* (**11a**). As described for **10a**, with **9a** (240 mg, 0.6 mmol) in CH_2Cl_2 (5 ml) and 3-chloroperbenzoic acid (80%; 160 mg, 0.72 mmol). FC (silica gel (20 g), pentane/Et_2O 1:1) afforded **11a** (quant.). Colorless foam. IR (CCl_4): 3070, 2960, 2900, 2860, 1745, 1430, 1375, 1345, 1225, 1195, 1160, 1140, 1110, 1065, 995, 985, 845. ^{1}H-NMR ($CDCl_3$): 1.05 (*s*, *t*-Bu); 1.41–1.50 (*m*, 1 H); 1.67–1.83 (*m*, 2 H); 1.89 (*d*, *J* = 12.9, 1 H); 2.43–2.52 (*m*, 2 H); 2.61–2.65 (*m*, 1 H); 2.69–2.77 (*m*, 1 H); 3.30 (*dd*, *J* = 8.2, 10.5, 1 H, CH_2O); 3.59 (*dd*, *J* = 5.2, 10.5, 1 H, CH_2O); 4.80–4.81 (*m*, H–C(1)); 7.35–7.46 (*m*, 6 arom. H); 7.61–7.65 (*m*, 4 arom. H); NOE: irrad. at 4.80–4.81 (H–C(1))→increase in intensitiy at 3.30, 3.59 (CH_2O). ^{13}C-NMR ($CDCl_3$): 19.23 (*s*, Me_3CSi); 26.84 (*q*, Me_3CSi); 32.16 (*d*); 32.99 (*t*); 33.81 (*t*); 40.33 (*t*); 47.74 (*d*); 65.13 (*t*, CH_2O); 82.68 (*d*, C(1)); 127.80 (*d*, CH, Ph_2Si); 129.84 (*d*, CH, Ph_2Si); 133.21 (*s*, C, Ph_2Si); 135.57 (*d*, CH, Ph_2Si); 170.70 (*s*, CO). MS: 394 (< 1, M^+), 338 (17), 337 (61), 279 (10), 231 (27), 200 (18), *199* (100), 197 (14), 183 (29), 181 (16), 161 (10), 139 (18), 135 (13), 121 (25), 105 (14), 93 (17), 91 (11), 77 (18), 41 (20).

*Methyl (1R,2S,4R)-2-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-4-hydroxycyclopentaneacetate* (**12a**). A soln. of **10a** (9.0 g, 22.8 mmol) in MeOH (200 ml) was treated at r.t. with a soln. of NaOMe (0.63 g, 11.7 mmol) in MeOH

(100 ml) and heated under reflux overnight. The pH of the mixture was adjusted to 6.6 with AcOH and the mixture adsorbed on silica gel (20 g). FC (silica gel (300 g), Et_2O) yielded enantiomerically enriched **12a** (9.3 g, 96%). Light yellow viscous oil. Anal. data: identical with those of racemic material [1].

Methyl (1R,2S,4S)-2-{[(tert-Butyl)diphenylsilyloxy]methyl}-4-(formyloxy)cyclopentaneacetate (**13a**). A soln. of **12a** (10.18 g, 23.9 mmol) and Ph_3P (9.4 g, 35.8 mmol) in THF (60 ml) was treated with HCOOH (1.35 ml, 35.8 mmol) at 0°. A soln. of diethyl azodicarboxylate (DEAD, 95%; 5.6 ml, 35.8 mmol) in THF (20 ml) was added within 30 min at 0°. Stirring was continued for 30 min at 0°, and the mixture was adsorbed on silica gel (20 g). FC (silica gel (400 g), pentane/Et_2O 2:1) yielded **13a** (10.2 g, 94%). Viscous oil.

Methyl (1R,2S,4S)-2-{[(tert-Butyl)diphenylsilyloxy]methyl}-4-hydroxycyclopentaneacetate (**14a**). A soln. of **13a** (10.2 g, 22.4 mmol) in MeOH (250 ml) was saturated with NH_3 at 0°. The mixture was stirred for 2.5 h at 0°, and the solvents were evaporated. Drying under high vacuum afforded enantiomerically enriched **14a** (9.6 g, quant.). Anal. data: identical with those of racemic material [1].

5-exo-[(Trityloxy)methyl]bicyclo[2.2.1]hept-2-ene ((±)-**3b**). A soln. of (±)-**2** (18.6 g, 150 mmol) in CH_2Cl_2 (400 ml) and pyridine (37 ml) was treated portionwise at r.t. with $Bu_4N(ClO_4)$ (61.5 g, 180 mmol) and TrCl (50.2 g, 180 mmol) and stirred at r.t. for 4.5 h. After addition of MeOH (40 ml), the mixture was stirred for 40 min, evaporated and then co-evaporated 3 times with toluene (100 ml). The precipitated ammonium salts were removed by filtration and washed well with toluene. The combined filtrate was adsorbed on silica gel (70 g). FC (silica gel (1000 g), petroleum ether/Et_3N 97:3) afforded (±)-**3b** (quant.). Colorless crystals. M.p. 65–66° (after recrystallization from hexane). IR (CCl_4): 3065, 2970, 2930, 2870, 1595, 1490, 1450, 1330, 1220, 1155, 1090, 1070, 1035, 930, 900, 705, 645, 635. ^{1}H-NMR ($CDCl_3$): 1.10 (*dt*, *J* = 11.6, 3.9, 1 H); 1.10 (*d*, *J* = 8.4, 1 H); 1.16–1.25 (*m*, 2 H); 1.71–1.78 (*m*, 1 H); 2.72 (br. *s*, 1 bridgehead H); 2.89 (br. *s*, 1 bridgehead H); 2.96 (*dd* (= '*t*'), *J* = 9.0, 1 H, CH_2O); 3.15 (*dd*, *J* = 6.2, 8.9, 1 H, CH_2O); 6.05 (*dd*, *J* = 3.0, 5.7, 1 olef. H); 6.14 (*dd*, *J* = 2.9, 5.7, 1 olef. H); 7.20–7.24 (*m*, 3 arom. H); 7.27–7.31 (*m*, 6 arom. H); 7.45–7.47 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 29.65 (*t*); 39.13 (*d*); 41.45 (*d*); 43.73 (*d*); 44.86 (*t*); 67.69 (*t*, CH_2O); 86.22 (*s*, Ph_3C); 126.80 (*d*, CH, *Ph*$_3$C); 127.67 (*d*, CH, *Ph*$_3$C); 128.75 (*d*, CH, *Ph*$_3$C); 136.65 (*d*, *C*H=CH); 136.72 (*d*, CH=*C*H); 144.47 (*s*, C, *Ph*$_3$C). MS: 366 (2, M^+), 244 (41), *243* (100), 165 (30), 105 (19), 57 (53), 56 (38), 43 (52), 42 (24), 41(68). Anal. calc. for $C_{27}H_{26}O$ (366.5): C 88.48, H 7.15; found: C 88.54, H 7.23.

(1R,2S,4R,5S)-5-[(Trityloxy)methyl]bicyclo[2.2.1]heptan-2-ol (**6b**) *and (1R,2S,4R,6R)-6-[(Trityloxy)-methyl]bicyclo[2.2.1]heptan-2-ol* (**7b**). To (+)-(1*R*)-α-pinene (80 ml, 506 mmol; $[\alpha]_D^{22°} = +47.1$, > 91% ee; freshly distilled from Na and benzophenone) was added 1.54M BH_3-THF (130 ml, 200 mmol) at 0°. The soln. was stirred for 48 h at 0°. After the precipitate ($(Ipc)_2BH$) settled, the supernatant was removed with a syringe. After cooling to −50°, (±)-**3b** (42 g, 115 mmol) in THF (40 ml) was added and the suspension stirred for 24 h at −25° and for 48 h at −5°. Workup as described for **6a** with 3N aq. NaOH (85 ml), 30% aq. H_2O_2 soln. (64 ml), and $NaHSO_3$ (20 g) and FC of the residue (in 2 portions on silica gel (1000 g), pentane/Et_2O/Et_3N 60:37:3) yielded enantiomerically enriched **6b** (22 g, 50%) and **7b** (20 g, 45%).

Data of **6b**: Colorless crystals. TLC (silica gel, pentane/Et_2O/Et_3N 60:37:3): R_f 0.18. M.p. 147° (after crystallization from toluene/hexane). 69% ee (measured by reaction with (+)-(*S*)-*Mosher*'s acid chloride [36] ($[\alpha]_D^{20°} = +135.5$ (*c* = 5.2, CCl_4); > 99% ee) in pyridine to a mixture of diastereoisomers (ratio from the ^{19}F-NMR integrals, 84.4:15.6). IR (KBr): 3430, 3060, 2960, 2830, 1590, 1490, 1450, 1220, 1155, 1115, 1065, 1005, 930, 900, 770, 750, 710, 695, 650, 635, 495. ^{1}H-NMR ($CDCl_3$): 0.88 (*dt*, *J* = 13.0, 4.8, 1 H); 1.02–1.06 (*m*, 1 H); 1.17 (*ddd*, *J* = 2.1, 8.6, 12.9, 1 H); 1.31–1.42 (*m*, 3 H, incl. OH); 1.62–1.69 (*m*, 1 H); 1.73 (*ddd*, *J* = 2.4, 6.9, 13.1, 1 H); 2.03 (br. *d*, *J* = 4.6, 1 bridgehead H); 2.35 (br. *d*, *J* = 4.2, 1 bridgehead H); 2.82 (*d*, *J* = 7.7, CH_2O); 3.75 (br. *d*, *J* = 6.8, H–C(2)); 7.19–7.30 (*m*, 9 arom. H); 7.42–7.44 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 28.95 (*t*); 31.03 (*t*); 37.73 (*d*); 41.11 (*d*); 42.69 (*t*); 44.25 (*d*); 66.83 (*t*, CH_2O); 74.66 (*d*, C(2)); 86.19 (*s*, Ph_3C); 126.84 (*d*, CH, *Ph*$_3$C); 127.69 (*d*, CH, *Ph*$_3$C); 128.74 (*d*, CH, *Ph*$_3$C); 144.41 (*s*, C, *Ph*$_3$C). MS: 384 (11, M^+), 307 (14), 297 (11), 245 (13), 244 (46), *243* (100), 241 (11), 228 (11), 184 (12), 183 (42), 166 (13), 165 (42), 107 (14), 106 (11), 105 (56), 91 (12), 85 (41), 81 (13), 79 (14), 77 (24), 67 (12), 57 (14), 55 (13), 43 (13), 41 (15). Anal. calc. for $C_{27}H_{28}O_2$ (384.5): C 84.34, H 7.34; found: C 83.96, H 7.31.

Data of **7b**: Colorless crystals. TLC (silica gel, pentane/Et_2O/Et_3N 60:37:3): R_f 0.25. M.p. 122° (after crystallization from Et_2O/pentane). IR (KBr): 3400, 3060, 2950, 2860, 1595, 1490, 1450, 1320, 1220, 1105, 1115, 1065, 1050, 1015, 900, 770, 750, 710, 695, 635. ^{1}H-NMR ($CDCl_3$): 0.80–0.88 (*m*, 1 H); 1.02–1.04 (*m*, 1 H); 1.17 (*ddd*, *J* = 2.2, 8.6, 11.2, 1 H); 1.26–1.32 (*m*, 1 H); 1.42–1.44 (*m*, 1 H); 1.50–1.67 (*m*, 3 H, incl. OH); 2.17 (br. *s*, 1 bridgehead H); 2.28 (br. *s*, 1 bridgehead H); 2.86 (*dd* (= '*t*'), *J* = 9.0, 1 H, CH_2O); 2.88 (*dd*, *J* = 6.5, 9.0, 1 H, CH_2O); 3.83 (br. *d*, *J* = 6.7, H–C(2)); 7.19–7.31 (*m*, 9 arom. H); 7.42–7.45 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 31.51 (*t*); 32.76 (*t*); 35.15 (*d*); 37.69 (*d*); 41.86 (*t*); 46.83 (*d*); 66.31 (*t*, CH_2O); 74.96 (*d*, C(2)); 86.25 (*s*, Ph_3C); 126.85 (*d*, CH, *Ph*$_3$C); 127.69 (*d*, CH, *Ph*$_3$C); 128.75 (*d*, CH, *Ph*$_3$C); 144.37 (*s*, C, *Ph*$_3$C). MS: 384 (11, M^+), 307 (14),

245 (14), 244 (48), *243* (100), 242 (10), 241 (13), 239 (12), 228 (12), 184 (15), 183 (51), 166 (20), 165 (59), 154 (11), 107 (14), 105 (50), 91 (12), 81 (17), 79 (18), 77 (27), 74 (11), 67 (19), 55 (12), 43 (20), 42 (10), 41 (23). Anal. calc. for $C_{27}H_{28}O_2$ (384.5): C 84.34, H 7.34; found: C 83.23, H 7.35.

(1R,4R,5S)-5-[(Trityloxy)methyl]bicyclo[2.2.1]heptan-2-one (**8b**). As described for **8a**, with **6b** (7.43 g, 19 mmol) in CH_2Cl_2 (270 ml), pyridinium chlorochromate (8.36 g, 39 mmol), *Celite* (12 g), and pyridine (4 ml) in CH_2Cl_2 (100 ml). Workup afforded **8b** as colorless crystals (quant.), which were recrystallized from Et_2O/hexane. M.p. 133–134°. IR (KBr): 3470, 3020, 2960, 2870, 1745, 1595, 1490, 1445, 1405, 1220, 1185, 1155, 1080, 960, 900, 780, 770, 750, 710, 635. ^{1}H-NMR ($CDCl_3$): 1.24 (*dt*, J = 13.3, 4.8, 1 H); 1.44–1.48 (*m*, 1 H); 1.54–1.56 (*m*, 1 H); 1.63 (*ddd*, J = 2.0, 8.6, 13.2, 1 H); 1.87 (*dd*, J = 4.2, 17.7, 1 H); 1.98–2.05 (*m*, 1 H); 2.11 (*dd*, J = 4.7, 17.8, 1 H); 2.48 (br. *d*, J = 4.4, 1 bridgehead H); 2.70 (br. *d*, J = 3.5, 1 bridgehead H); 2.96 (*dd* (= '*t*'), J = 9.1, 1 H, CH_2O); 3.02 (*dd*, J = 6.1, 9.2, 1 H, CH_2O); 7.21–7.32 (*m*, 9 arom. H); 7.42–7.45 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 28.18 (*t*); 34.44 (*t*); 37.51 (*d*); 40.54 (*d*); 45.51 (*t*); 49.74 (*d*); 66.33 (*t*, CH_2O); 86.44 (*s*, Ph_3C); 126.98 (*d*, CH, *Ph*$_3$C); 127.78 (*d*, CH, *Ph*$_3$C); 128.67 (*d*, CH, *Ph*$_3$C); 144.13 (*s*, C, *Ph*$_3$C); 218.03 (*s*, CO). MS: 382 (2, M^+), 244 (32), 243 (70), 242 (93), 241 (81), *240* (100), 239 (86), 238 (79), 237 (11), 236 (26), 229 (32), 228 (19), 227 (43), 226 (75), 225 (47), 224 (14), 216 (11), 215 (23), 214 (46), 213 (10), 212 (18), 203 (20), 202 (13), 201 (28), 200 (24), 199 (12), 190 (10), 188 (15), 187 (16), 182 (25), 180 (16), 167 (28), 166 (58), 165 (94), 164 (85), 163 (32), 153 (19), 152 (19), 105 (16), 95 (26), 79 (18), 77 (14). Anal. calc. for $C_{27}H_{26}O_2$ (382.5): C 84.78, H 6.85; found: C 84.56, H 6.57.

(1R,4R,6R)-6-[(Trityloxy)methyl]bicyclo[2.2.1]heptan-2-one (**9b**). As described for **8a**, with **7b** (5.0 g, 13 mmol) in CH_2Cl_2 (150 ml), pyridinium chlorochromate (5.6 g, 26 mmol), *Celite* (8 g), and pyridine (5 ml) in CH_2Cl_2 (100 ml). Workup afforded **9b** (4.64 g, 93%), which was crystallized from Et_2O/pentane. M.p. 109°. IR (KBr): 3430, 3060, 2950, 2875, 1745, 1595, 1490, 1450, 1410, 1300, 1230, 1165, 1065, 1035, 905, 770, 750, 705, 650, 635, 470. ^{1}H-NMR ($CDCl_3$): 1.23–1.29 (*m*, 1 H); 1.46–1.62 (*m*, 3 H); 1.84 (*dd*, J = 4.0, 17.8, 1 H); 2.00–2.07 (*m*, 1 H); 2.12–2.19 (*m*, 1 H); 2.57 (br. *s*, 1 bridgehead H); 2.68 (br. *s*, 1 bridgehead H); 2.95 (*dd* (= '*t*'), J = 8.9, 1 H, CH_2O); 3.02 (*dd*, J = 6.2, 9.1, 1 H, CH_2O); 7.20–7.31 (*m*, 9 arom. H); 7.41–7.44 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 32.06 (*t*); 34.39 (*t*); 35.19 (*d*); 36.75 (*d*); 44.84 (*t*); 52.45 (*d*); 65.41 (*t*, CH_2O); 86.50 (*s*, Ph_3C); 126.97 (*d*, CH, *Ph*$_3$C); 127.79 (*d*, CH, *Ph*$_3$C); 128.68 (*d*, CH, *Ph*$_3$C); 144.06 (*s*, C, *Ph*$_3$C); 217.64 (*s*, CO). MS: 382 (12, M^+), 305 (12), 244 (32), *243* (100), 234 (13), 183 (24), 166 (10), 165 (35), 105 (24), 95 (13), 81 (12), 79 (18), 77 (13), 67 (10), 41 (12). Anal. calc. for $C_{27}H_{26}O_2$ (382.5): C 84.78, H 6.85; found: C 84.81, H 6.76.

(1R,5R,6S)-6-[(Trityloxy)methyl]-2-oxabicyclo[3.2.1]octan-3-one (**10b**). As described for **10a**, with **8b** (15.7 g, 41 mmol), $NaHCO_3$ (6.9 g, 82 mmol), and 3-chloroperbenzoic acid (60%; 14.5 g, 49 mmol) in CH_2Cl_2 (350 ml). Workup with sat. $NaHCO_3$ soln. (185 ml) and 10% aq. $NaHSO_3$ soln. (35 ml) yielded, after crystallization from Et_2O/CH_2Cl_2/petroleum ether, **10b** (15.2 g, 93%). Colorless crystals. M.p. 151°. IR (KBr): 3450, 3060, 2960, 2910, 1740, 1595, 1490, 1450, 1375, 1225, 1200, 1055, 990, 900, 770, 750, 710, 635. ^{1}H-NMR ($CDCl_3$): 1.42–1.50 (*m*, 1 H); 1.61–1.69 (*m*, 1 H); 1.82 (br. *d*, J = 13.4, 1 H); 2.20–2.33 (*m*, 2 H); 2.45–2.47 (*m*, 1 H); 2.55 (*dt*, J = 18.5, 2.0, 1 H); 2.74 (*dd*, J = 5.0, 18.5, 1 H); 2.88–2.95 (*m*, 1 H, CH_2O); 3.02–3.07 (*m*, 1 H, CH_2O); 4.77–4.79 (*m*, H–C(1)); 7.21–7.33 (*m*, 9 arom. H); 7.38–7.43 (*m*, 6 arom. H); NOE: irrad. at 4.77–4.79 (H–C(1))→no increase in intensity at 2.88–3.07 (CH_2O). ^{13}C-NMR ($CDCl_3$): 33.66 (*t*); 34.41 (*d*); 36.60 (*t*); 41.22 (*t*); 42.90 (*d*); 66.01 (*t*, CH_2O); 81.14 (*d*, C(1)); 86.60 (*s*, Ph_3C); 127.08 (*d*, CH, *Ph*$_3$C); 127.84 (*d*, CH, *Ph*$_3$C); 128.61 (*d*, CH, *Ph*$_3$C); 143.96 (*s*, C, *Ph*$_3$C); 170.32 (*s*, CO). MS: 398 (10, M^+), 321 (11), 244 (31), *243* (100), 183 (34), 166 (10), 165 (57), 139 (12), 105 (63), 95 (12), 81 (10), 79 (11), 77 (34), 67 (14), 55 (12), 41 (26). Anal. calc. for $C_{27}H_{26}O_3$ (398.5): C 81.38, H 6.58; found: C 81.28, H 6.73.

(1R,5R,7S)-7-[(Trityloxy)methyl]-2-oxabicyclo[3.2.1]octan-3-one (**11b**). As described for **10a**, with **9b** (3.92 g, 10.3 mmol), $NaHCO_3$ (1.72 g, 20.5 mmol), and 3-chloroperbenzoic acid (60%; 3.54 g, 10.3 mmol) in CH_2Cl_2 (50 ml). Workup with sat. $NaHCO_3$ soln. (45 ml) and 10% aq. $NaHSO_3$ soln. (9 ml) yielded, after FC (silica gel (95 g), Et_2O/CH_2Cl_2 95:5) and crystallization from Et_2O, **11b** (3.17 g, 78%). Colorless crystals. M.p. 129°. IR (KBr): 3425, 3030, 2950, 1735, 1595, 1490, 1450, 1375, 1320, 1225, 1200, 1110, 1090, 1065, 1050, 1030, 985, 900, 780, 765, 755, 705, 635. ^{1}H-NMR ($CDCl_3$): 1.35–1.42 (*m*, 1 H); 1.55–1.61 (*m*, 1 H); 1.79–1.87 (*m*, 2 H); 2.43–2.49 (*m*, 2 H); 2.68 (*dd*, J = 2.6, 5.5, 1 H); 2.72–2.78 (*m*, CH_2O); 3.10 (*dd*, J = 4.0, 7.9, 1 H); 4.77–4.78 (*m*, H–C(1)); 7.21–7.32 (*m*, 9 arom. H); 7.39–7.42 (*m*, 6 arom. H); NOE: irrad. at 4.77–4.78 (H–C(1))→increase in intensity at 2.72–2.78 (CH_2O). ^{13}C-NMR ($CDCl_3$): 32.02 (*d*); 33.56 (*t*); 33.69 (*t*); 40.30 (*t*); 45.89 (*d*); 64.77 (*t*, CH_2O); 82.65 (*d*, C(1)); 86.68 (*s*, Ph_3C); 127.10 (*d*, CH, *Ph*$_3$C); 127.87 (*d*, CH, *Ph*$_3$C); 128.61 (*d*, CH, *Ph*$_3$C); 143.83 (*s*, C, *Ph*$_3$C); 170.58 (*s*, CO). MS: 398 (24, M^+), 321 (27), 259 (12), 258 (15), 245 (12), 244 (48), *243* (100), 242 (10), 241 (14), 239 (12), 228 (19), 184 (11), 183 (44), 166 (20), 165 (58), 139 (18), 106 (10), 105 (60), 95 (35), 91 (10), 85 (18), 81 (13), 79 (13), 77 (27), 67 (20), 55 (19), 43 (13), 42 (10), 41 (30). Anal. calc. for $C_{27}H_{26}O_3$ (398.5): C 81.38, H 6.58; found: C 81.09, H 6.44.

Methyl (1R,2S,4R)-4-Hydroxy-2-[(trityloxy)methyl]cyclopentaneacetate (**12b**). As described for **12a**, with **10b** (1.4 g, 3.5 mmol) and NaOMe (95 mg, 1.75 mmol) in MeOH (60 ml). The pH was adjusted to 8.5 with AcOH at 0°. The mixture was concentrated to $^1/_3$ of the original volume, taken up in Et_2O, washed with brine, dried ($MgSO_4$), and evaporated. FC (silica gel (30 g), petroleum ether/Et_2O/Et_3N 48:48:4) yielded **12b** (1.4 g, 93%). Viscous, colorless oil. IR ($CHCl_3$): 3610, 3060, 3000, 2950, 2860, 1730, 1595, 1490, 1450, 1440, 1380, 1180, 1150, 1070, 1030, 900. ^{1}H-NMR ($CDCl_3$): 1.38 (*dddd*, J = 1.7, 3.8, 7.1, 13.7, 1 H); 1.59 (*ddd*, J = 5.6, 10.0, 13.4, 1 H); 1.83–1.90 (*m*, 2 H, incl. OH); 2.01–2.11 (*m*, 1 H); 2.15–2.26 (*m*, 2 H); 2.38 (*dd*, J = 8.8, 15.6, 1 H); 2.60 (*dd*, J = 4.8, 15.6, 1 H); 3.02–3.09 (*m*, CH_2O); 3.61 (*s*, MeO); 4.26–4.30 (*m*, H–C(4)); 7.20–7.31 (*m*, 9 arom. H); 7.40–7.43 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 37.39 (*d*); 39.75 (*t*); 39.85 (*t*); 41.73 (*t*); 43.24 (*d*); 51.43 (*q*, MeO); 66.26 (*t*, CH_2O); 72.63 (*d*, C(4)); 86.47 (*s*, Ph_3C); 126.90 (*d*, CH, *Ph*$_3$C); 127.74 (*d*, CH, *Ph*$_3$C); 128.71 (*d*, CH, *Ph*$_3$C); 144.23 (*s*, C, *Ph*$_3$C); 173.74 (*s*, CO). MS: 430 (< 1, M^+), 260 (16), 259 (59), 245 (31), 244 (82), *243* (100), 242 (23), 241 (31), 239 (20), 228 (23), 215 (15), 188 (14), 187 (71), 183 (54), 172 (12), 171 (65), 169 (41), 167 (18), 166 (36), 165 (80), 155 (10), 154 (14), 153 (25), 151 (11), 139 (14), 137 (36), 121 (18), 105 (69), 95 (12), 93 (38), 91 (12), 81 (10), 79 (20), 77 (32), 67 (11), 55 (12), 44 (10), 43 (10), 41 (15).

Methyl (1R,2S,4S)-4-(Formyloxy)-2-[(trityloxy)methyl]cyclopentaneacetate (**13b**). As described for **13a**, with **12b** (1.4 g, 3.25 mmol), Ph_3P (1.25 g, 4.8 mmol), HCOOH (0.19 ml, 5.8 mmol), and DEAD (95%; 0.8 ml, 4.8 mmol) in THF (20 ml). FC (silica gel (30 g), petroleum ether/Et_2O/Et_3N 48:48:4) yielded **13b** (1.4 g, 94%). Viscous, slightly red oil.

Methyl (1R,2S,4S)-4-Hydroxy-2-[(trityloxy)methyl]cyclopentaneacetate (**14b**). As described for **14a**, with **13b** (650 mg, 1.4 mmol) in MeOH (20 ml). FC (silica gel (20 g), petroleum ether/Et_2O/Et_3N 48:48:4) yielded enantiomerically enriched **14b** (500 mg, 82%). Viscous colorless oil. IR ($CHCl_3$): 3610, 3060, 3000, 2950, 1730, 1600, 1490, 1450, 1440, 1150, 1070, 1025, 1000, 900. ^{1}H-NMR ($CDCl_3$): 1.39–1.51 (*m*, 1 H); 1.82–1.97 (*m*, 3 H, incl. OH); 2.12–2.19 (*m*, 1 H); 2.22 (*dd*, J = 8.6, 14.5, 1 H); 2.39–2.47 (*m*, 1 H); 2.51 (*dd*, J = 5.4, 9.0, 1 H); 3.14 (*dd*, J = 5.2, 9.1, 1 H, CH_2O); 3.18 (*dd*, J = 5.4, 9.1, 1 H, CH_2O); 3.61 (*s*, MeO); 4.22–4.27 (*m*, H–C(4)); 7.21–7.31 (*m*, 9 arom. H); 7.41–7.45 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 36.63 (*d*); 39.33 (*t*); 39.50 (*t*); 42.66 (*t*); 43.86 (*d*); 51.44 (*q*, MeO); 66.16 (*t*, CH_2O); 72.49 (*d*, C(4)); 86.96 (*s*, Ph_3C); 127.00 (*d*, CH, *Ph*$_3$C); 127.81 (*d*, CH, *Ph*$_3$C); 128.77 (*d*, CH, *Ph*$_3$C); 144.02 (*s*, C, *Ph*$_3$C); 173.25 (*s*, CO). MS: 430 (< 1, M^+), 260 (16), 259 (51), 245 (23), 244 (78), *243* (100), 242 (20), 241 (29), 239 (21), 228 (21), 215 (16), 187 (55), 184 (12), 183 (61), 171 (37), 168 (50), 167 (20), 166 (40), 165 (91), 154 (14), 153 (24), 152 (10), 149 (10), 139 (12), 137 (24), 121 (17), 115 (12), 107 (32), 106 (22), 105 (83), 97 (12), 95 (17), 93 (47), 91 (20), 81 (16), 79 (32), 78 (14), 77 (59), 75 (10), 74 (14), 69 (15), 67 (22), 59 (23), 58 (12), 57 (10), 55 (24), 53 (10), 51 (14), 45 (15), 43 (46), 42 (11), 41 (43). Anal. calc. for $C_{28}H_{30}O_4$ (430.54): C 78.11, H 7.02; found: C 78.66, H 7.42.

Methyl t-*4-[(2′R)-2′-Acetoxy-2′-phenylacetoxy]*-t-*2-*{[(tert-*butyl)diphenylsilyloxy]methyl*}*cyclopentane*-r-*1-acetate* ((−)-**15a**/(−)-**16a**). DEAD (95%; 0.85 ml, 5.20 mmol) was added at 0° over 1 h to a soln. of (±)-**12a** (1.83 g, 4.30 mmol), Ph_3P (1.36 g, 5.20 mmol), and (−)-(*R*)-*O*-acetylmandelic acid (1.00 g, 5.20 mmol) in THF (10 ml). The mixture was stirred at r.t. for 3 h. Evaporation and FC (silica gel (170 g), CH_2Cl_2/AcOEt 199:1) yielded a 1:1 mixture of (−)-**15a** and (−)-**16a** (quant.). Pure isomers were obtained by prep. TLC (silica gel, eluted 4 times with CH_2Cl_2).

Data of (1R,2S,2′R,4S)-diastereoisomer (−)-**15a**: TLC (silica gel, CH_2Cl_2/AcOEt 95:5): R_f 0.57. $[\alpha]_D^{20°} = -22.4$ (c = 4.4, $CHCl_3$). IR (CCl_4): 3070, 2960, 2930, 2860, 1750, 1590, 1470, 1430, 1370, 1230, 1210, 1175, 1110, 1080, 1060, 940, 700. ^{1}H-NMR ($CDCl_3$): 1.06 (*s*, *t*-Bu); 1.49 (*ddd*, J = 6.0, 9.7, 13.9, 1 H); 1.64–1.71 (*m*, 1 H); 1.76–1.87 (*m*, 2 H); 2.06–2.24 (*m*, 6 H, incl. *s* at 2.17, Ac); 2.46–2.55 (*m*, 1 H); 3.51–3.64 (*m*, 5 H, incl. *s* at 3.57, CH_2O, MeO); 5.15–5.20 (*m*, H–C(4)); 5.81 (*s*, H–C(2′)); 7.32–7.45 (*m*, 11 arom. H); 7.64–7.67 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 19.26 (*s*, Me_3C); 20.69 (*q*, *Me*CO); 26.89 (*q*, Me_3C); 35.15 (*t*); 36.84 (*d*); 38.81 (*t*); 39.10 (*t*); 45.80 (*d*); 51.37 (*q*, MeO); 66.46 (*t*, CH_2O); 74.64 (*d*, C(4)); 76.95 (*d*, C(2′)); 127.48 (*d*, CH, *Ph*C); 127.70 (*d*, CH, Ph_2Si); 128.74 (*d*, CH, *Ph*C); 129.09 (*d*, CH, *Ph*C); 129.68 (*d*, CH, Ph_2Si); 133.66 (*s*, C, Ph_2Si); 133.86 (*s*, C, *Ph*C); 135.63 (*d*, CH, Ph_2Si); 168.39 (*s*, CO); 170.21 (*s*, CO); 172.89 (*s*, *C*OOMe). MS: 571 (5, $[M - MeO]^+$), 545 (13), 486 (13), 485 (34), 453 (11), 352 (15), 351 (45), 347 (30), 333 (26), 291 (11), 241 (36), 214 (15), 213 (78), 200 (16), 199 (81), 197 (26), 195 (28), 183 (35), 182 (10), 181 (41), 168 (14), *167* (100), 153 (55), 149 (18), 139 (17), 137 (10), 135 (52), 121 (29), 118 (26), 107 (76), 105 (23), 93 (51), 91 (39), 79 (57), 77 (25), 57 (11), 43 (92), 41 (11).

Data of (1S,2R,2′R,4R)-diastereoisomer (−)-**16a**: TLC (silica gel, CH_2Cl_2/AcOEt 95:5): R_f 0.54. $[\alpha]_D^{20°} = -32.6$ (c = 4.1, $CHCl_3$). IR (CCl_4): 3070, 2950, 2930, 2855, 1745, 1470, 1430, 1370, 1230, 1175, 1110, 1080, 1060, 905, 700. ^{1}H-NMR ($CDCl_3$): 1.02 (*s*, *t*-Bu); 1.31 (*dddd*, J = 1.4, 3.5, 7.2, 14.2, 1 H); 1.59 (*ddd*, J = 6.1, 10.0, 13.8, 1 H); 1.71–2.00 (*m*, 1 H); 2.05–2.19 (*m*, 6 H, incl. *s* at 2.15, Ac); 2.23–2.31 (*m*, 1 H); 2.59 (*dd*, J = 4.1, 14.8, 1 H); 3.41 (*dd*, J = 6.3, 10.2, 1 H, CH_2O); 3.44 (*dd*, J = 6.5, 10.0, 1 H, CH_2O); 3.62 (*s*, MeO); 5.16–5.22 (*m*, H–C(4)); 5.81 (*s*, H–C(2′)); 7.27–7.30 (*m*, 3 arom. H); 7.34–7.46 (*m*, 8 arom. H); 7.60–7.63 (*m*, 4 arom. H). ^{13}C-NMR

($CDCl_3$): 19.23 (*s*, Me_3C); 20.72 (*q*, *Me*CO); 26.89 (*q*, Me_3C); 35.34 (*t*); 37.39 (*d*); 38.98 (*t*); 39.17 (*t*); 45.67 (*d*); 51.47 (*q*, MeO); 66.74 (*t*, CH_2O); 74.68 (*d*, C(4)); 76.85 (*d*, C(2')); 127.57 (*d*, CH, *Ph*C); 127.70 (*d*, CH, Ph_2Si); 128.74 (*d*, CH, *Ph*C); 129.16 (*d*, CH, *Ph*C); 129.71 (*d*, CH, Ph_2Si); 133.72 (*s*, C, Ph_2Si); 133.82 (*s*, C, *Ph*C); 135.63 (*d*, CH, Ph_2Si); 168.42 (*s*, CO); 170.27 (*s*, CO); 173.02 (*s*, *C*OOMe). MS: 571 (5, $[M - MeO]^+$), 485 (19), 352 (11), 351 (31), 347 (23), 333 (18), 241 (18), 213 (48), 199 (48), 197 (16), 195 (16), 183 (22), 181 (26), 167 (66), 153 (39), 149 (12), 139 (14), 135 (39), 121 (24), 118 (19), 107 (62), 105 (18), 93 (47), 91 (34), 79 (57), 77 (25), 57 (12), *43* (100), 41 (12).

*Methyl (1R,2S,4S)-2-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-4-hydroxycyclopentaneacetate* ((+)-**14a**). NaOMe (74 ml, 30% in MeOH) was added at r.t. to a soln. of (−)-**15a** (253 mg, 0.4 mmol) in MeOH (5 ml). The mixture was stirred at r.t. for 17 h. The solvents were evaporated, and the residue was purified by FC (silica gel (15 g), CH_2Cl_2/AcOEt 19:1): pure (+)-**14a** (160 mg, 89%). Viscous colorless oil. Anal. data: identical with those of enantiomerically enriched **14a**. $[\alpha]_D^{20°} = +3.7$ (c = 16.0, $CHCl_3$).

Methyl (1R,2S,4S)-4-[(2'R)-2'-Acetoxy-2'-phenylacetoxy]-2-[(trityloxy)methyl]cyclopentaneacetate ((−)-**15b**). As described for (−)-**15a**, with **12b** (69% ee; 2.10 g, 4.88 mmol), Ph_3P (1.67 g, 6.34 mmol), DEAD (95%; 1.1 ml, 6.34 mmol), and (−)-(*R*)-*O*-acetylmandelic acid (1.23 g, 6.34 mmol) in THF (10 ml). FC (silica gel (300 g), petroleum ether/Et_2O/Et_3N 49:49:2) yielded a mixture (2.64 g, 89%) of (−)-**15b** (83%) and **16b** (17%; by NMR). Pure isomer (−)-**15b** was separated by prep. TLC (silica gel, eluted 3 times with CH_2Cl_2). $[\alpha]_D^{20°} = -19.1$ (c = 3.6, $CHCl_3$). IR ($CHCl_3$): 3060, 3030, 2950, 1745, 1600, 1490, 1450, 1435, 1325, 1235, 1215, 1180, 1155, 1060, 1030, 1000, 900. ^{1}H-NMR ($CDCl_3$): 1.47 (*ddd*, J = 6.0, 9.6, 14.0, 1 H); 1.64 (*dddd*, J = 1.4, 3.6, 7.5, 14.3, 1 H); 1.76–1.88 (*m*, 2 H); 1.95–2.05 (*m*, 1 H); 2.07–2.19 (*m*, 4 H, incl. *s* at 2.16, Ac); 2.26 (*ddd*, J = 6.3, 8.9, 14.8, 1 H); 2.50 (*dd*, J = 4.4, 14.9, 1 H); 3.41 (*dd*, J = 6.3, 10.2, 1 H); 3.03–3.11 (*m*, CH_2O); 3.56 (*s*, MeO); 5.15–5.19 (*m*, H–C(4)); 5.74 (*s*, H–C(2')); 7.21–7.33 (*m*, 14 arom. H); 7.41–7.44 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 20.69 (*q*, *Me*CO); 35.78 (*t*); 37.26 (*d*); 38.87 (*t*); 39.02 (*t*); 43.89 (*d*); 51.40 (*q*, MeO); 66.25 (*t*, CH_2O); 74.62 (*d*, C(4)); 76.82 (*d*, C(2')); 86.59 (*s*, Ph_3C); 126.97 (*d*, arom. CH); 127.45 (*d*, arom. CH); 127.79 (*d*, arom. CH); 128.70 (*d*, arom. CH); 128.75 (*d*, arom. CH); 129.06 (*d*, arom. CH); 133.80 (*s*, arom. C); 144.19 (*s*, C, Ph_3C); 168.37 (*s*, CO); 170.23 (*s*, CO); 172.86 (*s*, *C*OOMe). MS: 606 (< 1, M^+), 347 (11), 259 (18), 244 (65), *243* (100), 241 (11), 169 (24), 165 (40), 153 (13), 107 (12), 105 (14).

Methyl (1R,2S,4S)-4-Hydroxy-2-[(trityloxy)methyl]cyclopentaneacetate ((−)-**14b**). As described for (+)-**14a**, with (−)-**15b** (36 mg, 0.06 mmol) and NaOMe (10 ml; 30% in MeOH) in MeOH (5 ml). FC (silica gel (4 g), petroleum ether/Et_2O/Et_3N 37:60:3) yielded pure (−)-**14b** (21 mg, 82%). Viscous colorless oil. Anal. data: identical with those of enantiomerically enriched **14b**. $[\alpha]_D^{20°} = -1.2$ (c = 2.1, $CHCl_3$).

5'-[(Acetylthio)methyl]-N^6*-benzoyl-3'-{[(*tert*-butyl)diphenylsilyloxy]methyl}-2',3',5'-trideoxy-1'a-carba-adenosine* (= *(1R,2S,4R)-S-{4-[6-(Benzoylamino)-9H-purin-9-yl]-2-{[(*tert*-butyl)diphenylsilyloxy]methyl}-cyclopentaneethyl} Thioacetate*; **17**). Starting from enantiomerically enriched **14a**, see [1]. Anal. data: identical with those of racemic material.

N^2*-Isobutyryl-2',3',5'-trideoxy-5'-(methoxycarbonyl)-*O^6*-[2-(4-nitrophenyl)ethyl]-3'-[(trityloxy)methyl]-1'a-carbaguanosine* (= *Methyl (1R,2S,4R)-4-{2-Isobutyramido-6-[2-(4-nitrophenyl)ethoxy]-9H-purin-9-yl}-2-[(trityloxy)methyl]cyclopentaneacetate*; **19**). A suspension of finely powdered N^2-isobutyryl-O^6-[2-(4-nitrophenyl)ethyl]guanine (**18**; 370 mg, 1.0 mmol) in anh. dioxane (15 ml) was heated under reflux for 30 min and, after cooling to r.t., treated with a soln. of Ph_3P (350 mg, 1.33 mmol) and enantiomerically enriched **14b** (273 mg, 0.63 mmol; 69% ee) in THF (10 ml). DEAD (95%; 0.22 ml, 1.33 mmol) was added over 30 min and the mixture stirred at r.t. overnight. Adsorption on silica gel (4.5 g) and FC (silica gel (140 g), petroleum ether/AcOEt 8:2) yielded **19** (353 mg, 71%). Lightly colored foam.

N^2*-Isobutyryl-2',3',5'-trideoxy-5'-(methoxycarbonyl)-3'-[(trityloxy)methyl]-1'a-carbaguanosine* (= *Methyl (1R,2S,4R)-4-(1,6-Dihydro-2-isobutyramido-6-oxo-9H-purin-9-yl)-2-[(trityloxy)methyl]cyclopentaneacetate*; **20**). A soln. of **19** (0.35 g, 0.45 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.13 ml, 0.9 mmol) in pyridine (10 ml) was stirred at r.t. overnight. After several co-evaporations with toluene, the residue was adsorbed on silica gel (2 g). FC (silica gel (45 g), CH_2Cl_2/MeOH 96:4) yielded **20** (269 mg, 95%) as a colorless foam, which could be crystallized from CH_2Cl_2/pentane. M.p. 212–216° (slow dec. > 202°). UV (0.159 mg in 10 ml): 207 (40100), 260 (15700), 280 (sh, 10300). IR (KBr): 3430, 3190, 3060, 2970, 2950, 1735, 1680, 1610, 1560, 1475, 1450, 1400, 1255, 1190, 1155, 1070, 950, 900, 785, 765, 750, 710, 635. ^{1}H-NMR ($CDCl_3$): 1.25 (*d*, J = 6.0, 6 H, Me_2CHCO); 1.85 (*dt*, J = 12.6, 9.8, 1 H); 2.09–2.20 (*m*, 3 H); 2.26–2.35 (*m*, 1 H); 2.42 (*dd*, J = 9.3, 15.3, 1 H); 2.49 (*dt*, J = 14.2, 7.1, 1 H); 2.57–2.68 (*m*, 2 H, incl. Me_2CHCO); 3.12 (*dd*, J = 5.0, 9.3, 1 H, CH_2O); 3.18 (*dd*, J = 4.6, 9.3, 1 H, CH_2O); 3.62 (*s*, MeO); 4.64–4.72 (*m*, H–C(1')); 7.22–7.33 (*m*, 9 arom. H); 7.42–7.45 (*m*, 6 arom. H); 7.63 (*s*, H–C(8)); 8.57 (*s*, NH–C(2)); 11.94 (br. *s*, NH(1)). ^{13}C-NMR ($CDCl_3$): 18.97 (*q*, Me_2CHCO); 35.71 (*t*); 36.53 (*d*, Me_2CHCO); 37.68 (*d*, C(4')); 38.71 (*t*); 38.89 (*t*); 43.36 (*d*, C(3')); 51.66 (*s*, MeO); 54.45 (*d*, C(1')); 65.34 (*t*, CH_2O); 76.73 (*s*, Ph_3C);

121.80 (*s*, C(5)); 127.11 (*d*, CH, Ph_3C); 127.87 (*d*, CH, Ph_3C); 128.71 (*d*, CH, Ph_3C); 137.31 (*d*, C(8)); 144.00 (*s*, C, Ph_3C); 146.83, 148.13 (*s*, C(2), C(6)); 155.67 (*s*, C(4)); 173.09 (*s*, COO); 178.24 (*s*, CON). FAB-MS (3-nitrobenzyl alcohol): 634 ($[M + 1]^+$). Anal. calc. for $C_{37}H_{39}N_5O_5$ (633.75): C 70.12, H 6.20, N 11.05; found: C 70.28, H 6.35, N 10.95.

*N⁶-Benzoyl-3'-{[(*tert*-butyl)diphenylsilyloxy]methyl}-2',3',5'-trideoxy-5'-(mercaptomethyl)-1'a-carbaadenosine* (= *(1*R,*2*S,*4*R*)-4-[6-(Benzoylamino)-9*H*-purin-9-yl]-2-{[(*tert*-butyl)diphenylsilyloxy]methyl}cyclopentaneethanethiol*; **21**). A soln. of enantiomerically enriched **17** (542 mg, 0.8 mmol) in MeOH (80 ml) was degassed by repeated freeze-thawing under high vacuum. The clear soln. was then saturated with NH_3 at 0°. The mixture was allowed to stand at 0° for 30 min and then evaporated (cold-water bath). FC (silica gel (60 g), CH_2Cl_2/acetone 8:2) yielded **21** (350 mg, 69%). Colorless foam. UV (0.195 mg in 10 ml): 205 (44500), 281 (20200). IR (KBr): 3410, 3070, 2960, 2939, 2860, 1700, 1610, 1580, 1515, 1455, 1430, 1390, 1335, 1315, 1250, 1115, 1030, 825, 800, 745, 705, 650, 615, 505. ^{1}H-NMR ($CDCl_3$): 1.10 (*s*, *t*-Bu); 1.31 (*t*, *J* = 7.6, SH); 1.64–1.72 (*m*, 1 H); 1.80–1.90 (*m*, 2 H); 2.03–2.18 (*m*, 2 H); 2.29–2.58 (*m*, 5 H); 3.65 (*dd*, *J* = 5.6, 10.3, 1 H, CH_2O); 3.71 (*dd*, *J* = 4.7, 10.3, 1 H, CH_2O); 4.88–4.96 (*m*, H–C(1')); 7.38–7.47 (*m*, 6 arom. H); 7.49–7.53 (*m*, 2 arom. H); 7.57–7.61 (*m*, 1 H); 7.67–7.70 (*m*, 4 arom. H); 8.01 (*s*, purine H); 8.02–8.04 (*m*, 2 arom. H); 8.78 (*s*, purine H); 9.12 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 19.34 (*s*, Me_3CSi); 23.22 (*t*); 27.00 (*q*, Me_3CSi); 34.66 (*t*); 39.07 (*d*, C(4')); 39.28 (*t*); 39.63 (*t*); 45.35 (*d*, C(3')); 55.06 (*d*, C(1')); 65.84 (*t*, CH_2O); 123.61 (*s*, C(5)); 127.81 (*d*, CH, Ph_2Si); 127.89 (*d*, CH, Bz); 128.86 (*d*, CH, Bz); 129.85 (*d*, CH, Ph_2Si); 132.73 (*d*, CH, Bz); 133.46 (*s*, C, Ph_2Si); 133.79 (*s*, C, Bz); 135.67 (*d*, CH, Ph_2Si); 141.45 (*d*, C(8)); 149.44 (*s*, C(4)); 152.21 (*s*, C(6)); 152.28 (*d*, C(2)); 164.68 (*s*, CO). FAB-MS (3-nitrobenzyl alcohol): 636 ($[M + 1]^+$).

*3'-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-2',3',5'-trideoxy-5'-(mercaptomethyl)-1'a-carbaadenosine* (= *(1*R,*2*S,*4*R*)-4-(6-Amino-9*H*-purin-9-yl)-2-{[(*tert*-butyl)diphenylsilyloxy]methyl}cyclopentaneethanethiol*; **22**). A soln. of enantiomerically enriched **17** (897 mg, 1.33 mmol) in MeOH (110 ml) was degassed by repeated freeze-thawing under high vacuum, and then saturated with NH_3 at 0°. The mixture was allowed to stand at r.t. for 3 h and then evaporated (cold-water bath). FC (silica gel (110 g), CH_2Cl_2/acetone 7:3) yielded **22** (628 mg, 89%). Colorless foam. UV (0.082 mg in 5 ml): 208 (34900), 261 (14900). IR (KBr): 3440, 3320, 3160, 2930, 2860, 1640, 1600, 1570, 1470, 1430, 1410, 1360, 1330, 1305, 1250, 1110, 1090, 1010, 825, 800, 740, 700, 650, 615. ^{1}H-NMR ($CDCl_3$): 1.08 (*s*, *t*-Bu); 1.29 (*t*, *J* = 7.7, SH); 1.60–1.70 (*m*, 1 H); 1.78 (*dd*, *J* = 10.9, 22.8, 1 H); 1.81–1.88 (*m*, 1 H); 1.98–2.06 (*m*, 1 H); 2.08–2.15 (*m*, 1 H); 2.28–2.31 (*m*, 2 H); 2.35–2.46 (*m*, 1 H); 2.47–2.75 (*m*, 2 H); 3.63 (*dd*, *J* = 5.9, 10.2, 1 H, CH_2O); 3.69 (*dd*, *J* = 5.0, 10.2, 1 H, CH_2O); 4.80–4.89 (*m*, H–C(1')); 5.82 (br. *s*, NH_2); 7.38–7.47 (*m*, 6 arom. H); 7.66–7.69 (*m*, 4 arom. H); 7.82 (*s*, purine H); 8.35 (*s*, purine H). ^{13}C-NMR ($CDCl_3$): 19.28 (*s*, Me_3CSi); 23.19 (*t*); 26.95 (*q*, Me_3CSi); 34.65 (*t*); 39.17 (*d*, C(4')); 39.45 (*t*); 39.68 (*t*); 45.37 (*d*, C(3')); 54.57 (*d*, C(1')); 65.92 (*t*, CH_2O); 120.13 (*s*, C(5)); 127.75 (*d*, CH, Ph_2Si); 129.78 (*d*, CH, Ph_2Si); 133.46 (*s*, C, Ph_2Si); 135.63 (*d*, CH, Ph_2Si); 138.74 (*d*, C(8)); 150.15 (*s*, C(4)); 152.63 (*d*, C(6)); 155.60 (*s*, C(2)). FAB-MS (3-nitrobenzyl alcohol): 532 ($[M + 1]^+$).

*N⁶-Benzoyl-3'-{[(*tert*-butyl)diphenylsilyloxy]methyl}-2',3',5'-trideoxy-5'-[(tritylthio)methyl]-1'a-carbaadenosine* (= *(1*R,*2*S,*4*R*)-4-[6-(Benzoylamino)-9*H*-purin-9-yl]-2-{[(*tert*-butyl)diphenylsilyloxy]methyl}cyclopentaneethyl Trityl Sulfide*; **23**). A soln. of **21** (180 mg, 0.28 mmol) in CH_2Cl_2 (3 ml) was treated at r.t. with TrCl (312 mg, 1.12 mmol) in pyridine (1 ml). The mixture was stirred at r.t. overnight and quenched with MeOH (2 ml). Evaporation and FC (silica gel (30 g), CH_2Cl_2/MeOH 99:1) yielded **23** (198 mg, 80%). Colorless foam. UV (1.0 mg in 50 ml): 206 (83500), 280 (12100). IR (KBr): 3420, 3060, 2930, 2860, 1705, 1610, 1580, 1510, 1490, 1450, 1430, 1390, 1310, 1250, 1160, 1185, 1110, 1030, 830, 800, 745, 700, 620, 510. ^{1}H-NMR ($CDCl_3$): 1.08 (*s*, *t*-Bu); 1.31–1.43 (*m*, 1 H); 1.50–1.70 (*m*, 2 H); 1.90–2.00 (*m*, 2 H); 2.08–2.32 (*m*, 5 H); 3.50 (*dd*, *J* = 5.3, 10.2, 1 H, CH_2O); 3.61 (*dd*, *J* = 4.6, 10.2, 1 H, CH_2O); 4.80–4.86 (*m*, H–C(1')); 7.14–7.27 (*m*, 9 arom. H); 7.33–7.46 (*m*, 12 arom. H); 7.48–7.62 (*m*, 3 arom. H); 7.64–7.68 (*m*, 4 arom. H); 7.94 (*s*, purine H); 8.02–8.04 (*m*, 2 arom. H); 8.78 (*s*, purine H); 9.14 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 19.33 (*s*, Me_3CSi); 26.97 (*q*, Me_3CSi); 30.56 (*t*); 34.19 (*t*); 34.83 (*t*); 39.18 (*t*); 39.44 (*d*, C(4')); 45.35 (*d*, C(3')); 54.90 (*d*, C(1')); 65.81 (*t*, CH_2O); 66.72 (*s*, Ph_3C); 123.50 (*s*, C(5)); 126.60 (*d*, arom. CH); 127.77 (*d*, arom. CH); 127.86 (*d*, 2 arom. CH); 128.84 (*d*, arom. CH); 129.61 (*d*, arom. CH); 129.78 (*d*, arom. CH); 132.71 (*d*, arom. CH); 133.46 (*s*, arom. C); 133.79 (*s*, arom. C); 135.64 (*d*, arom. CH); 141.39 (*d*, C(8)); 144.89 (*s*, C, Ph_3C); 149.31 (*s*, C(4)); 152.22 (*s*, *d*, overlapping, C(2), C(6)); 164.70 (*s*, CO). FAB-MS (3-nitrobenzyl alcohol): 878 ($[M + 1]^+$).

N⁶-Benzoyl-2',3',5'-trideoxy-3'-(hydroxymethyl)-5'-[(tritylthio)methyl]-1'a-carbaadenosine (= *(1*S,*2*R,*4*R*)-4-[6-(Benzoylamino)-9*H*-purin-9-yl]-2-[2-(tritylthio)ethyl]cyclopentanemethanol*; **24**). A soln. of **23** (160 mg, 0.18 mmol) and $Bu_4NF \cdot 3\ H_2O$ (63 mg, 0.2 mmol) in THF (2 ml) was stirred at r.t. overnight. The mixture was adsorbed on silica gel (800 mg) and submitted to FC (silica gel (40 g), CH_2Cl_2/MeOH 95:5): **24** (105 mg, 91%). Colorless foam. UV (0.085 mg in 5 ml): 206 (46300), 281 (19600). IR (KBr): 3410, 3055, 2920, 1700, 1610, 1580, 1510, 1490, 1450, 1400, 1310, 1250, 1180, 1160, 1075, 1030, 800, 745, 700, 645. ^{1}H-NMR ($CDCl_3$): 1.40–1.50 (*m*, 1 H); 1.59 (*tt* (= '*q*'), *J* = 11.1, 1 H); 1.66–1.72 (*m*, 1 H); 1.76–1.86 (*m*, 1 H); 1.92–2.01 (*m*, 1 H); 2.13–2.33 (*m*, 7 H);

3.45–3.51 (*m*, 1 H, CH_2OH); 3.58–3.63 (*m*, 1 H, CH_2OH); 4.77–4.86 (*m*, H–C(1')); 7.17–7.21 (*m*, 3 arom. H); 7.25–7.29 (*m*, 6 arom. H); 7.39–7.42 (*m*, 6 arom. H); 7.48–7.52 (*m*, 2 arom. H); 7.56–7.61 (*m*, 1 arom. H); 7.97 (*s*, purine H); 8.01–8.03 (*m*, 2 arom. H); 8.77 (*s*, purine H); 9.20 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 30.54 (*t*); 34.13 (*t*); 34.94 (*t*); 39.09 (*t*); 39.40 (*d*, C(4')); 45.35 (*d*, C(3')); 54.74 (*d*, C(1')); 64.84 (*t*, CH_2OH); 66.80 (*s*, Ph_3C); 123.39 (*s*, C(5)); 126.67 (*d*, CH, Ph_3C); 127.89 (*d*, CH, Ph_3C); 127.93 (*d*, CH, Bz); 128.82 (*d*, CH, Bz); 129.59 (*d*, CH, Ph_3C); 132.72 (*d*, Bz); 133.76 (*s*, C, Bz); 141.26 (*d*, C(8)); 144.82 (*s*, C, Ph_3C); 149.50 (*s*, C(4)); 152.04 (*s*, C(6)); 152.26 (*d*, C(2)); 164.81 (*s*, CO). FAB-MS (3-nitrobenzyl alcohol): 640 ($[M + 1]^+$).

N^6-*Benzoyl-2',3',5'-trideoxy-3'-[(methylsulfonyloxy)methyl]-5'-[(tritylthio)methyl]-1'a-carbaadenosine* (= *(1S,2R,4R)-4-[6-(Benzoylamino)-9H-purin-9-yl]-2-[2-(tritylthio)ethyl]cyclopentanemethyl Methanesulfonate*; **25**). A soln. of **24** (80 mg, 0.13 mmol) in CH_2Cl_2 (1.5 ml) and pyridine (100 µl) was treated at 0° with methanesulfonyl chloride (30 µl, 0.39 mmol) and stirred at r.t. for 3 h. The crude product was adsorbed on silica gel (200 mg) and rapidly isolated by FC (silica gel (10 g), CH_2Cl_2/MeOH 97:3): **25** (quant.). Colorless foam.

Coupling. A soln. of **21** (16 mg, 0.025 mmol) and **25** (18 mg, 0.025 mmol) in DMF (1 ml) was degassed by repeated freeze-thawing under vacuum. After addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 8 µl, 0.05 mmol), the mixture was stirred at r.t. for 5 h. Further DBU (8 µl, 0.05 mmol) was added and stirring continued at r.t. for 24 h. After filtration through silica gel, the major product was isolated by prep. TLC (silica gel, CH_2Cl_2/MeOH 97:3) to yield a mixture (9 mg) of N^6-*benzoyl-2',3',5'-trideoxy-5'-[(tritylthio)methyl]-1'a-carbaadenylyl-(3' → CH_2SCH_2 → 5')-N^6-benzoyl-3'-{[(*tert*-butyl)diphenylsilyloxy]methyl}-2',3',5'-trideoxy-1'a-carbaadenosine* (**26**) and a disulfide derived from **21**. FAB-MS (3-nitrobenzyl alcohol): 1258 (M^+ of **26**), 1270 (M^+ of disulfide).

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