Total Synthesis of (−)-Lithospermoside[1])

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The total synthesis of the naturally occurring noncyanogenic cyanoglucoside (−)-lithospermoside (**1**) was achieved starting from optically pure oxatrinorbornenone (+)-**2** in 12 steps and 10% overall yield. The key step of the synthesis, the glycosidation, turned out to be very sensitive to steric hindrance, and we had, therefore, to optimize the choice of the protection used for the two other OH functions of the aglycone. Finally, the desired β-D-glucoside **15** was obtained in a very good yield (72%) under *Koenigs–Knorr*-glycosidation conditions, closely related to those used for the total synthesis of (−)-bauhinin.

Introduction. – The first isolation of (−)-lithospermoside (**1**) was realized in 1955 by *Sosa* and co-workers from the roots of *Lithospermum purpureo-caeruleum* [2a]. Twenty-two years later, the same research group also found (−)-lithospermoside in the roots of *L. officinale* and proposed a structure based on NMR data [2b]. In 1976, *Dwuma-Badu et al.* isolated a cyanoglucoside from the roots of a leguminous plant growing in western Africa, *Griffonia simplicifolia*; they called it griffonin and proposed a structure [3]. But, in 1979, *Wu et al.* [4] found that both (−)-lithospermoside and griffonin were identical to a cyanoglucoside they had previously isolated from *Thalictrum rugosum* and *T. revolutum*. The structures proposed by *Sosa* and co-workers and *Dwuma-Badu et al.* differed only in the absolute configuration of the aglycone moiety; therefore, circular dichroism studies allowed *Wu et al.* to ascertain this configuration [4] (which turned out to be that proposed by *Sosa* and co-workers). (−)-Lithospermoside was also found in the barks of *Cercis siliquastrum* [5a] and, together with (−)-menisdaurin, in the leaves of *Cowania mexicana* by *Itoh et al.* [5b]. They studied the biological properties and concluded that both lithospermoside and menisdaurin are of biological importance as antitumor promoters.

A number of other noncyanogenic cyanoglucosides of related structure, *e.g.*, simmondsin, bauhinin, purshianin, and dasycarponin, have been isolated [6] from various medicinal plants, and, since these cyanoglucosides are of biological importance, they appeared to us to be interesting targets for total synthesis.

We report here the first total synthesis of (−)-lithospermoside (**1**) that takes advantage of the versatile methodologies developed during our first synthesis of a cyanoglucoside, (−)-bauhinin [7].

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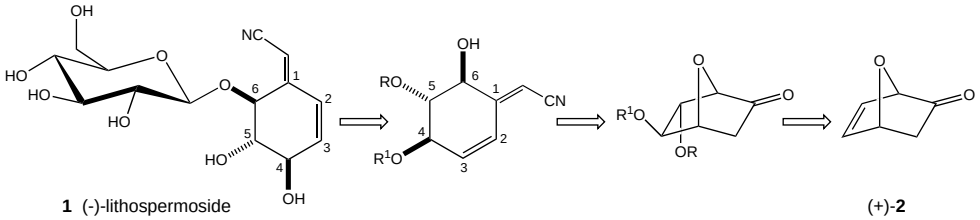
[1]) For a preliminary communication, see [1].

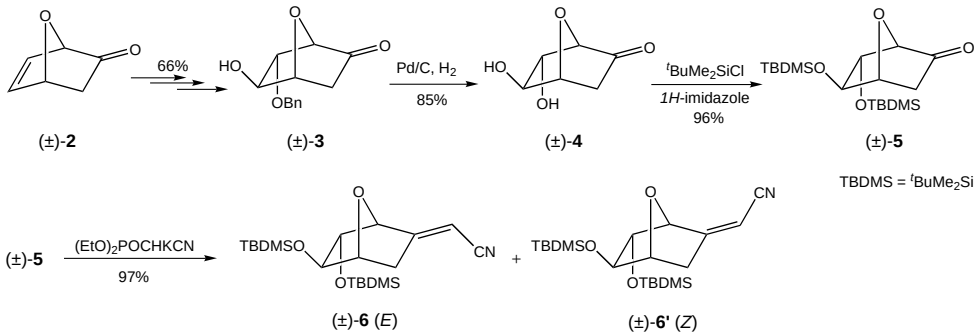
Synthesis. – To achieve the total synthesis of (−)-lithospermoside, we had to choose, for the two OH functions at C(4) and C(5) of the aglycone moiety, protecting groups compatible with both the synthesis of this aglycone and the glycosidation reaction (see *Scheme 1*). Our starting material is the oxatrinorbornenone (+)-**2** (*Vogel*'s 'naked sugar'), which is easily obtained enantiomerically pure [8] and whose powerful synthetic potentialities have already been demonstrated during the syntheses of many biologically active substances [9].

Scheme 1



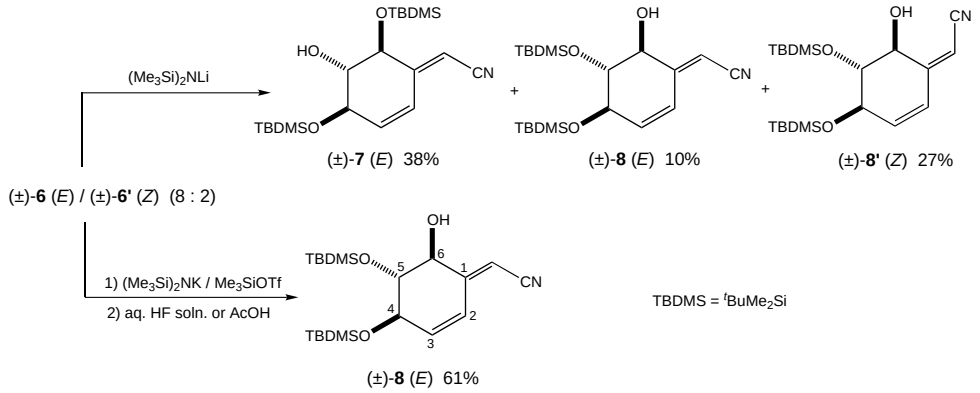
Since we had devised, for the synthesis of (−)-bauhinin [7], 'neutral' glycosidation conditions that tolerate the presence of an acid-sensitive *tert*-butyldimethylsilyl ether [10], we chose the same protecting group for the synthesis of the aglycone moiety of (−)-lithospermoside. The hydroxy ketone (±)-**3** was easily obtained [11] in three steps and 66% total yield from (±)-**2**. The benzyl protecting group had to be replaced at this stage since conjugated C=C bonds would be introduced in the following steps and, therefore, the silyl diether (±)-**5** was prepared *via* (±)-**4** according to our previous procedure [9b] (see *Scheme 2*). An 8 : 2 mixture of nitriles (±)-**6**/(±)-**6′** was obtained by a *Wittig–Horner* reaction.

Scheme 2



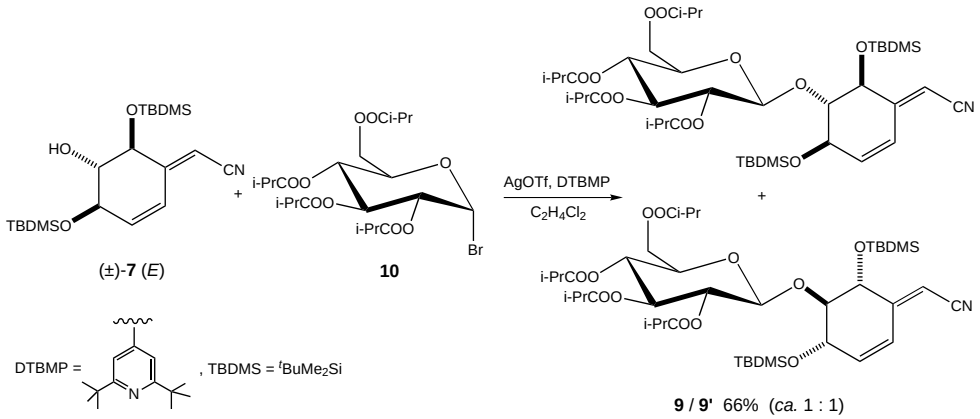
Then the oxa-bridge-opening reaction was carried out in basic medium [12a] with the unseparated nitrile mixture (±)-**6**/(±)-**6′** since identical results were obtained with both the (*E*)- and (*Z*)-isomer. To avoid the formation of the undesired compound (±)-**7** resulting from a 1,2-silyl ether migration [12b], this reaction was carried out in the presence of Me_3SiOTf, which reacted immediately with the intermediate potassium alcoholate (see *Scheme 3*) [12c]. Under these optimized reaction conditions (see *Exper.*

Scheme 3



Part), the desired protected aglycone (±)-**8** was obtained in 61% yield from (±)-**6**/(±)-**6′**, and the formation of the (*Z*)-isomer (±)-**8′** was avoided. The hydroxynitrile (±)-**8** could not be glycosidated under the *Koenigs–Knorr* conditions developed previously in our laboratory [7][10], despite numerous attempts[2]): (±)-**8** was quantitatively recovered. On the other hand, glycosidation under the same conditions of the isomeric hydroxynitrile (±)-**7** (see *Scheme 4*) afforded the two diastereoisomeric β-D-glucosides **9**/**9′** in good yield (66% for the 2 isomers; not optimized).

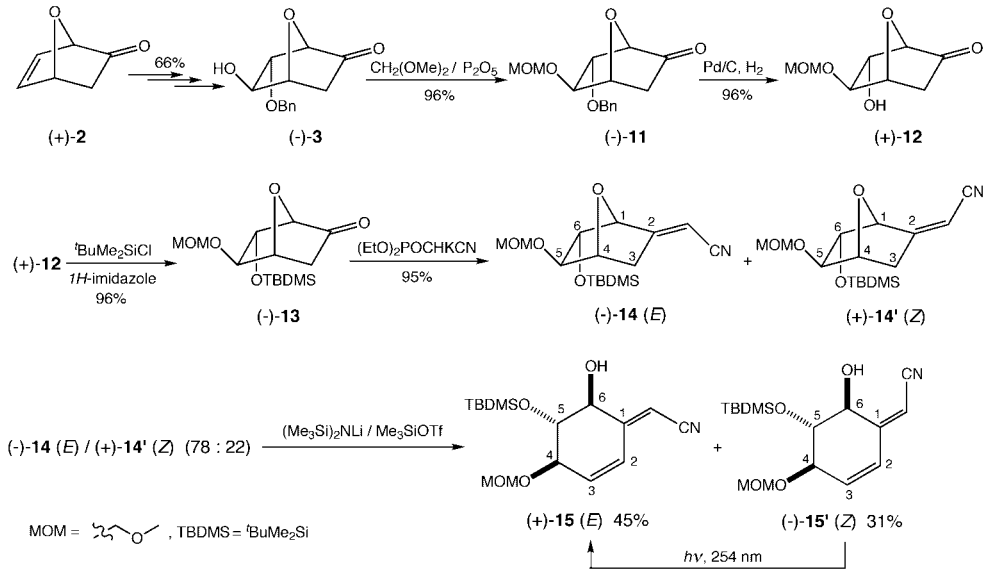
Scheme 4



[2]) Glycosidation of the (*Z*)-isomer (±)-**8′** was also unsuccessful, as it could be expected from previous results [7].

It seemed us that the steric hindrance of the bulky silyl ether at C(4) could be responsible for the low reactivity of OH–C(6) of the protected aglycone (±)-**8** (see *Scheme 3*) since, for the synthesis of (–)-bauhinin [7], an aglycone differing from **8** only in the presence of a MeO group at C(4) instead of this silyl ether, the OH group was easily glycosidated. We had, therefore, to use another protecting group at C(4), and we chose the unbulky methoxymethyl (MOM) group, which, furthermore, should be compatible with all synthetic steps. The MOM group was easily introduced under acidic conditions [13] in hydroxy ketone (–)-**3** at the outset of the synthesis (→(–)-**11**; see *Scheme 5*), and the benzyl protecting group was then replaced by a silyl ether (→(+)-**12**→(–)-**13**).

Scheme 5



For (±)-**6**/(±)-**6′**, the opening of the oxa bridge was carried out with the nitrile mixture (–)-**14**/(+)-**14′**, since identical results were obtained with both isomers[3]). This bridge-opening reaction had to be optimized to yield[4]) 45% of (+)-**15** (*E*) and 31% of (–)-**15′** (*Z*), since it was found to be very sensitive to experimental conditions: to limit degradation and silyl ether migration, nitriles (–)-**14**/(+)-**14′** should be added to a solution of base/Me_3SiOTf and not the reverse (see *Exper. Part*). Despite many attempts, conditions analogous to those used for (±)-**6**/(±)-**6′**, which avoided the formation of the (*Z*)-isomer, gave here much lower yields of (+)-**15**. Dienenitrile (–)-

[3]) The configuration of the C=C bond could be unambiguously determined by ^{1}H-NMR nuclear-*Overhauser*-effect (NOE) measurements: irradiation of C=CHCN of (–)-**14** enhanced H–C(1) by 7.5%, but H_{endo}–C(3) and H_{exo}–C(3) were enhanced by less than 0.2%; irradiation of C=CHCN of (+)-**14′** enhanced H_{endo}–C(3) by 1.7%, H_{exo}–C(3) by 1.5%, and H–C(1) by less than 0.2%.

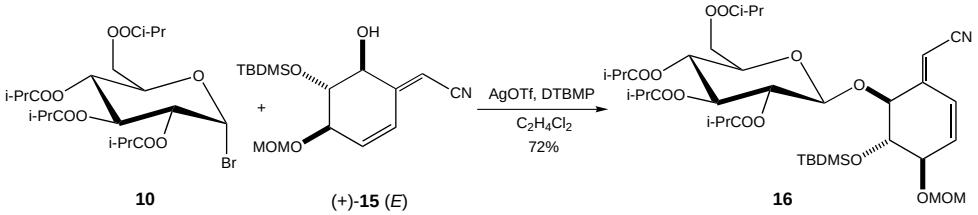
[4]) The configuration of the exocyclic C=C bond was determined by ^{1}H-NMR NOE measurements: irradiation of C=CHCN of (+)-**15** enhanced H–C(6) by 2.5% and H–C(2) by less than 0.2%; irradiation of C=CHCN of (–)-**15′** enhanced H–C(2) by 12% and H–C(6) by less than 0.2%.

15′ has the (*Z*)-configuration of natural (−)-lithospermoside but is much less stable than the (*E*)-isomer (+)-**15**, and glycosidation attempts were unsuccessful, affording only starting material and degradation products. The glycosidation was, therefore, carried out with the (*E*)-isomer (+)-**15**, the C=C bond being photoisomerized at the end of the synthesis. Consequently, the (*Z*)-isomer (−)-**15′** had to be isomerized to the (*E*)-isomer (+)-**15** by irradiation with an Hg lamp.

To keep degradation to a minimum and, thus, to achieve maximal recovery, irradiation was stopped well before the stationary state between the two isomers was reached[5]): in a typical single run, 29% of (+)-**15** (*E*) was obtained and 57% of (−)-**15′** (*Z*) recovered. Four successive irradiations allowed us to transform the (*Z*)-isomer (−)-**15′** into the (*E*)-isomer (+)-**15** with 60% yield (see *Exper. Part*). The yield of (+)-**15** (*E*) was thereby brought to 63% from (−)-**14**/(+)-**14′** and to 52% for the five steps from (−)-**3**.

Under the *Koenigs-Knorr*-glycosidation conditions optimized during the total synthesis of (−)-bauhinin [7], β-D-glucoside **16** was easily obtained in 72% yield (see *Scheme 6*), and no orthoester formation was observed. It should be noted that the two expected diastereoisomeric β-D-glucosides were obtained in very different yields during the glycosidation of racemic (±)-**15**: 37% of **16** and 19% of the β-D-glucoside of (−)-**15.**

Scheme 6



DTBMP = 2,6-di(*tert*-butyl)-4-methylpyridine, TBDMS = ^{t}BuMe$_2$Si

Hexaacetate **17** was prepared[6]) from **16** in 79% yield, without isolation of the intermediates, by successive treatments with $BF_3 \cdot Et_2O/Me_2S$ [14], MeONa, and Ac_2O/pyridine (see *Scheme 7*).

Irradiation of **17** with a Hg lamp afforded a mixture[7]) of the (*E*)- and (*Z*)-isomers **17** and **17′**. As for (+)-**15**/(−)-**15′**, irradiation was stopped well before the stationary

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5) Isomerization experiments starting from both pure (*E*)- and (*Z*)-isomers turned out to give identical results: if degradation is to be kept below 10%, irradiation should be stopped in both cases once a 2:1 mixture of starting material/other isomer was obtained.

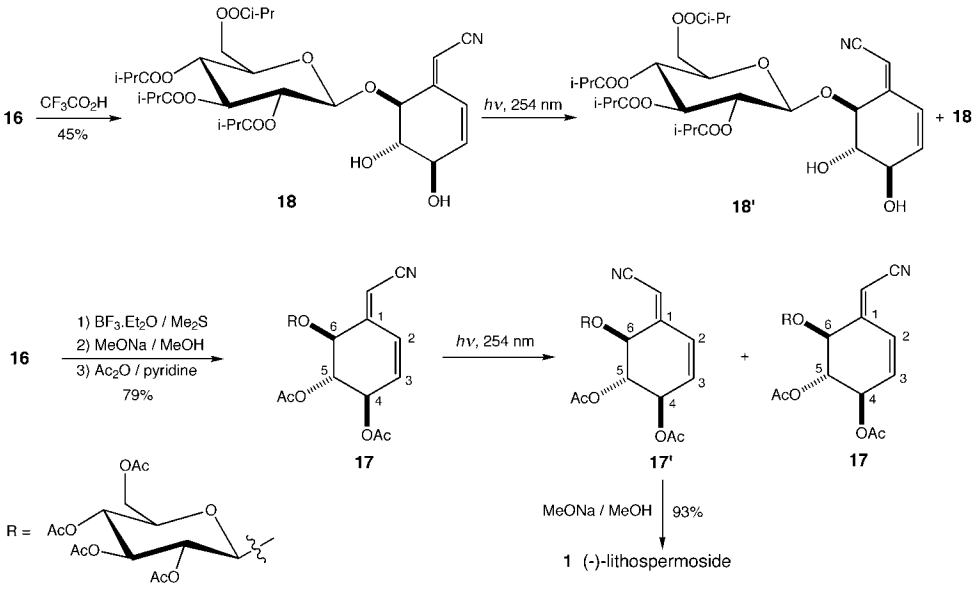
6) We chose to carry out the photoisomerization step with acetate **17** and not with diol **18** since the two isomers **18** and **18′** could not be separated by column chromatography. Moreover, **18** was obtained from **16** with only a modest yield probably because of partial cleavage of the ester groups (see *Scheme 7*).

7) The configuration of the exocyclic C=C bond was confirmed by ^{1}H-NMR NOE measurements : irradiation of C=CHCN of **17** enhanced H−C(6) by 4% and H−C(2) by only 2%; irradiation of C=CHCN and H−C(4) of **17′** enhanced H−C(2) by 9% and H−C(6) by only 2.5%. With C_6D_6 as solvent instead of $CDCl_3$, it was possible to irradiate selectively C=CHCN of **17′**, and H−C(2) was then enhanced by 14.5%.

state between the two isomers was reached: in a typical single run, 24% of **17′** were obtained and 60% of **17**/**17′** 96:4 recovered. Four successive irradiations allowed us to isomerize the (*E*)-isomer **17** into the (*Z*)-isomer **17′** with 51% yield (see *Exper. Part*).

Hydrolysis of hexaacetate **17′** in basic medium yielded (−)-lithospermoside (**1**). The data of **17′** and **1** were identical to those reported [2b][3][4] for the natural compound.

Scheme 7



Conclusions. – The synthesis of (−)-lithospermoside, a cyanoglucoside found in several medicinal plants, was achieved in 12 steps and with 10% overall yield from oxatrinorbornenone (+)-**2**, thanks, especially, to the versatile glycosidation procedure developed in our laboratory [10].

The senior author would like to thank Prof. *P. Vogel*, Lausanne, in whose laboratory the work on cyanoglucosides was begun. We are grateful also to the *Centre National de la Recherche Scientifique* (UMR Q 7015), for financial support, and to Dr. *D. Le Nouen* and Dr. *S. Bourg* for the recording of many NMR spectra.

Experimental Part

1. *General.* See [10][15].

2. *Total Synthesis of (−)-Lithospermoside* (**1**). *(−)-(1*R,*4*R,*5*R,*6*S*)-6*-endo-*(Benzyloxy)-5*-exo-*(methoxymethoxy)-7-oxabicyclo[2.2.1]heptan-2-one* ((−)-**11**). $CH_2(OMe)_2$ (124 ml, 1.40 mol) and P_2O_5 (10 g) were added to a soln. of (−)-**3** (3.3 g, 14.1 mmol) in anh. $CHCl_3$ (50 ml). The mixture was stirred for 1 h at 20°, then sat. aq. $NaHCO_3$ soln. (100 ml) was added dropwise (vigorous gas evolution!). The mixture was extracted twice with AcOEt (300 ml), the org. phase washed with sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated, and the residue purified by CC (silica gel, AcOEt/petroleum ether 3:7): (−)-**11** (3.75 g, 96%). White crystals. M.p. 69–70° ((±)-**11** (obtained from (±)-**3**), m.p. 49–51°). $[\alpha]_D^{25} = -10.3$ ($c = 1$, $CHCl_3$). IR (KBr): 2938, 2908, 2872, 1769, 1460, 1453, 1401, 1385, 1338, 1311, 1229, 1210, 1154, 1109, 1019, 977, 913. ^{1}H-NMR ($CDCl_3$, 250 MHz): 2.13 (*d*, $^2J = 17.8$, H_{endo}–C(3)); 2.50 (*dd*, $^2J = 17.8$, $^3J = 6.7$, H_{exo}–C(3)); 3.39 (*s*, MeO); 3.95 (*s*, H–C(5)); 4.05 (*d*,

$^3J = 5.5$, H–C(6)); 4.43 (*d*, $^3J = 5.5$, H–C(1)); 4.57 (*AB*, $^2J = 11.6$, $\nu_o\delta = 27.6$, PhCH_2); 4.69 (br. *s*, OCH_2O); 4.80 (*d*, $^3J = 6.7$, H–C(4)); 7.30–7.35 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz): 39.01 (C(3)); 55.68 (MeO); 72.49 (PhCH_2); 80.29, 80.74, 82.83, 83.44 (C(1), C(4), C(5), C(6)); 95.84 (OCH_2O); 127.96, 128.09, 128.49 (3 arom. CH); 136.75 (arom. C); 207.27 (C(2)). Anal. calc. for $C_{15}H_{18}O_5$ (278.30): C 64.74, H 6.52; found: C 64.82, H 6.39.

*(+)-(1*R*,4*R*,5*S*,6*S*)-6*-endo-*Hydroxy-5*-exo-*(methoxymethoxy)-7-oxabicyclo[2.2.1]heptan-2-one* ((+)-**12**). To a soln. of (–)-**11** (3.75 g, 13.47 mmol) in AcOEt (80 ml), 10% Pd/C (300 mg) was added. The mixture was stirred for 15 h under H_2 at 20°. After filtration over *Celite*® and washing of the *Celite*® with AcOEt, the combined filtrates were evaporated, and the residue was purified by CC (silica gel, AcOEt/petroleum ether 1:1): (+)-**12** (2.42 g, 96%). Colorless oil ((±)-**12** (obtained from (±)-**11**), colorless oil). $[\alpha]_D^{25} = +22$ ($c = 3.4$, $CHCl_3$). IR (CCl_4): 3425, 2936, 2902, 1769, 1407, 1259, 1249, 1153, 1107, 1077, 1050, 1014, 948, 917, 900, 785. ^{1}H-NMR ($CDCl_3$, 250 MHz): 2.13 (*d*, $^2J = 17.9$, H_{endo}–C(3)); 2.54 (*ddd*, $^2J = 17.9$, $^3J = 6.6$, $^4J = 1.1$, H_{exo}–C(3)); 3.44 (*s*, MeO); 3.83 (*s*, H–C(5)); 4.32–4.34 (*m*, H–C(1), H–C(6)); 4.7–4.8 (*m*, H–C(4), OCH_2O). ^{13}C-NMR ($CDCl_3$, 62.9 MHz): 39.49 (C(3)); 55.74 (MeO); 76.45 (C(6)); 81.04, 81.36 (C(4), C(5)); 85.39 (C(1)); 95.94 (OCH_2O); 209.19 (C(2)). Anal. calc. for $C_8H_{12}O_5$ (188.18): C 51.06, H 6.43; found: C 51.24, H 6.66.

*(–)-(1*R*,4*R*,5*R*,6*S*)-6*-endo-*{[(*tert-*Butyl)dimethylsilyl]oxy}-5*-exo-*(methoxymethoxy)-7-oxabicyclo[2.2.1]-heptan-2-one* ((–)-**13**). A soln. of (+)-**12** (2.4 g, 12.7 mmol), ^{t}BuMe$_2$SiCl (2.5 g, 16.6 mmol), and 1*H*-imidazole (1.56 g, 22.9 mmol) in DMF (20 ml) was stirred at 20° for 15 h and then poured in a mixture of AcOEt (300 ml) and sat. aq. $NaHCO_3$ soln. (60 ml). The org. phase was dried ($MgSO_4$) and evaporated and the resulting oil purified by CC (silica gel, AcOEt/petroleum ether 1:9): (–)-**13** (3.69 g, 96%). Colorless oil ((±)-**13** (obtained from (±)-**12**), m.p. 41–42°). $[\alpha]_D^{25} = -14$ ($c = 5.3$, $CHCl_3$). IR (CCl_4): 2957, 2928, 2899, 2857, 1767, 1475, 1395, 1262, 1254, 1142, 1119, 1106, 1088, 1046, 1019, 995, 984, 946, 930, 855, 841. ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.07, 0.08 (2*s*, Me_2Si); 0.86 (*s*, ^{t}BuSi); 2.05 (*d*, $^2J = 17.7$, H_{endo}–C(3)); 2.44 (*ddd*, $^2J = 17.7$, $^3J = 6.6$, $^4J = 1.3$, H_{exo}–C(3)); 3.40 (*s*, MeO); 3.78 (*s*, H–C(5)); 4.17 (*d*, $^3J = 5.8$, H–C(6)); 4.22 (br. *d*, $^3J = 5.8$, H–C(1)); 4.73 (*m*, OCH_2O, H–C(4)). ^{13}C-NMR ($CDCl_3$, 62.9 MHz): –5.13, –5.04 (Me_2Si); 17.84 (Me_3CSi); 25.54 (*Me*$_3$CSi); 38.82 (C(3)); 55.67 (MeO); 77.54 (C(6)); 80.57, 81.33 (C(4), C(5)); 86.11 (C(1)); 95.95 (OCH_2O); 206.73 (C(2)). Anal. calc. for $C_{14}H_{26}O_5Si$ (302.44): C 55.60, H 8.67; found: C 55.56, H 8.62.

*(–)-(2*E*)- and (+)-(2*Z*)-{(1*S*,4*R*,5*R*,6*R*)-6*-endo-*{[(*tert-*Butyl)dimethylsilyl]oxy}-5*-exo-*(methoxymeth-oxy)-7-oxabicyclo[2.2.1]hept-2-ylidene}acetonitrile* ((–)-**14** and (+)-**14′**, resp.). Anh. THF (10 ml) was added to KH (969 mg, 24.2 mmol) prepared by three successive washings with petroleum ether of a 20% KH dispersion in oil. Under a stream of Ar, the suspension was cooled to 0°, and $(EtO)_2P(O)CH_2CN$ (4 ml, 25.4 mmol) was added dropwise under stirring. At the end of H_2 evolution (*ca.* 10 min), a soln. of (–)-**13** (3.65 g, 12.06 mmol) in anh. THF (10 ml) was added dropwise. The cooling bath was removed and the mixture left for 15 min at 20° under stirring. The reaction was quenched with sat. aq. $NaHCO_3$ soln. (30 ml), and the mixture was extracted twice with AcOEt (50 ml). The org. phase was dried ($MgSO_4$) and evaporated and the residue purified by CC (silica gel, AcOEt/petroleum ether 1:9): (–)-**14** (2.7 g, 74%) followed by (+)-**14′** (766 mg, 21%).

*Data of (*E*)-Isomer* (–)-**14**: Colorless oil ((±)-**14** (obtained from (±)-**13**), m.p. 51–52°). $[\alpha]_D^{25} = -77.4$ ($c =$ 4, $CHCl_3$). UV (MeCN): 212.4 (14600). IR (CCl_4): 3069, 2997, 2905, 2856, 2224, 1660, 1472, 1463, 1425, 1253, 1189, 1155, 1133, 1112, 1061, 1039, 1021, 1008, 990, 983, 944, 859, 839. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.06, 0.07 (2*s*, Me_2Si); 0.85 (*s*, ^{t}BuSi); 2.46 (*dd*, $^2J = 17.7$, $^4J = 2.2$, H_{endo}–C(3)); 2.74 (*ddd*, $^2J = 17.7$, $^3J = 6.1$, $^4J = 2.9$, H_{exo}–C(3)); 3.40 (*s*, MeO); 3.50 (*d*, $^3J = 1.3$, H–C(5)); 4.17 (br. *d*, $^3J = 5.3$, H–C(6)); 4.61 (br. *d*, $^3J = 5.3$, H–C(1)); 4.64 (br. *d*, $^3J = 6.1$, H–C(4)); 4.70 (*AB*, $^2J = 7.1$, $\nu_o\delta = 4.1$, OCH_2O); 5.30 (br. *dd*, $^4J = 2.9$, 2.2, C=CHCN). ^{13}C-NMR ($CDCl_3$, 62.9 MHz): –4.97, –4.93 (Me_2Si); 17.82 (Me_3CSi); 25.57 (*Me*$_3$CSi); 35.11 (C(3)); 55.70 (MeO); 79.15, 81.53, 81.99 (C(4), C(5), C(6)); 86.00 (C(1)); 92.96 (C=*C*HCN); 96.12 (OCH_2O); 116.07 (CN); 163.15 (C(2)). Anal. calc. for $C_{16}H_{27}NO_4Si$ (325.48): C 59.04, H 8.36, N 4.30; found: C 58.70, H 8.35, N 4.32.

*Data of (*Z*)-Isomer* (+)-**14′**: White solid. M.p. 53–55° ((±)-**14′** (obtained from (±)-**13**), m.p. 46–48°). $[\alpha]_D^{25} = +97.1$ ($c = 1$, $CHCl_3$). UV (MeCN): 212.6 (13200). IR (KBr): 2957, 2856, 2221, 1660, 1470, 1423, 1381, 1362, 1258, 1210, 1155, 1131, 1109, 1066, 1045, 1015, 984, 942, 922, 890, 854, 840, 800. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.12, 0.15 (2*s*, Me_2Si); 0.89 (*s*, ^{t}BuSi); 2.33 (br. *d*, $^2J = 17.4$, H_{endo}–C(3)); 2.63, (*ddd*, $^2J = 17.4$, $^3J =$ 6.1, $^4J = 2.2$, H_{exo}–C(3)); 3.40 (*s*, MeO); 3.48 (*d*, $^3J = 1.3$, H–C(5)); 4.24 (br. *d*, $^3J = 5.4$, H–C(6)); 4.60 (br. *d*, $^3J = 6.1$, H–C(4)); 4.70 (*AB*, $^2J = 7.1$, $\nu_o\delta = 7.6$, OCH_2O); 4.95 (br. *d*, $^3J = 5.4$, H–C(1)); 5.36 (br. *s*, C=CHCN). ^{13}C-NMR ($CDCl_3$, 62.9 MHz): –5.29, –5.15 (Me_2Si); 17.93 (Me_3CSi); 25.65 (*Me*$_3$CSi); 35.16 (C(3)); 55.76 (MeO); 79.22, 81.22, 81.51 (C(4), C(5), C(6)); 86.27 (C(1)); 93.01 (C=*C*HCN); 96.23 (OCH_2O); 116.27 (CN); 162.85 (C(2)). Anal. calc. for $C_{16}H_{27}NO_4Si$ (325.48): C 59.04, H 8.36, N 4.30; found: C 59.19, H 8.46, N 4.38.

*(+)-(2*E*)- and (−)-(2*Z*)-{(4*R*,5*R*,6*S*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-hydroxy-4-(methoxymethoxy)-cyclohex-2-en-1-ylidene}acetonitrile* ((+)-**15** and (−)-**15′**, resp.). a) *Opening of the Oxa Bridge.* A soln. of (−)-**14**/(+)-**14′** 78:22 (400 mg, 1.23 mmol) in anh. THF (1 ml) was added, under Ar, to a mixture of Me_3SiOTf (680 µl, 3.75 mmol) and 1M $(Me_3Si)_2NLi$ in THF (7 ml, 7 mmol) at −5°. After stirring at −5° for 6.5 min, sat. aq. NH_4Cl soln. (25 ml) and aq. 1M HCl (10 ml) were successively added, and the mixture was extracted twice with AcOEt (100 ml). The org. phase was washed with sat. aq. $NaHCO_3$ soln. (25 ml), dried ($MgSO_4$), and evaporated and the residue purified by CC (silica gel, AcOEt/petroleum ether 1:9): successively (+)-**15** (180 mg, 45%) and (−)-**15′** (123 mg, 31%).

*Data of (*E*)-Isomer* (+)-**15**: Colorless oil ((±)-**15** (obtained from (±)-**14**/(±)-**14′**), colorless oil). $[\alpha]_D^{25} = +95$ ($c = 1.8$, $CHCl_3$). UV (MeCN): 258.5 (19500). IR (CCl_4): 3485, 2953, 2936, 2889, 2857, 2216, 1602, 1550, 1473, 1380, 1375, 1251, 1149, 1099, 1045, 992, 902, 937, 780. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.11, 0.13 (2*s*, Me_2Si); 0.92 (*s*, *t*BuSi); 2.68 (*d*, $^3J = 2.5$, OH−C(6)); 3.42 (*s*, MeO); 3.61 (*dd*, $^3J = 10$, 7.5, H−C(5)); 4.10 (br. *d*, $^3J = 7.5$, H−C(4)); 4.20 (br. *d*, $^3J = 10$, H−C(6)); 4.76 (*AB*, $^2J = 6.9$, $\nu_o\delta = 28.4$, OCH_2O); 5.57 (*d*, $^4J = 1$, C=CHCN); 6.18 (*dd*, $^3J = 10$, $^4J = 1$, H−C(2)); 6.59 (*dd*, $^3J = 10$, 2.2, H−C(3)). ^{13}C-NMR ($CDCl_3$, 100.57 MHz): −4.69, −4.17 (Me_2Si); 18.12 (Me_3CSi); 25.85 (Me_3CSi); 55.73 (MeO); 72.51 (C(6)); 77.44 (C(4)); 80.36 (C(5)); 93.09 (C=*C*HCN); 98.45 (OCH_2O); 116.63 (CN); 123.94 (C(3)); 137.67 (C(2)); 156.16 (C(1)). Anal. calc. for $C_{16}H_{27}NO_4Si$ (325.48): C 59.04, H 8.36, N 4.30; found: C 59.08, H 8.44, N 4.26.

*Data of (*Z*)-Isomer* (−)-**15′**: Yellow oil ((±)-**15′** (obtained from (±)-**14**/(±)-**14′**), m.p. 75–77°). $[\alpha]_D^{25} = -76$ ($c = 1.2$, $CHCl_3$). UV (MeCN): 258.5 (22700). IR (CCl_4): 3450, 2952, 2930, 2889, 2857, 2216, 1602, 1550, 1473, 1380, 1375, 1251, 1149, 1099, 1045, 992, 902, 837, 780. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.11, 0.14 (2*s*, Me_2Si); 0.87 (*s*, *t*BuSi); 3.13 (*d*, $^3J = 6.3$, OH−C(6)); 3.41 (*s*, MeO); 3.92 (*dd*, $^3J = 7.4$, 5.7, H−C(5)); 4.07 (*dddd*, $^3J = 5.7$, 3.2, $^4J = 1.2$, $^6J = 0.7$, H−C(4)); 4.49 (*ddd*, $^3J = 7.4$, 6.3, $^4J = 1.6$, H−C(6)); 4.74 (*AB*, $^2J = 6.8$, $\nu_o\delta = 13.5$, OCH_2O); 5.33 (*dq*, $^4J = 1.6$, 0.7, $^5J = 0.7$, $^6J = 0.7$, C=CHCN); 6.13 (*ddd*, $^3J = 10$, 3.2, $^5J = 0.7$, H−C(3)); 6.19 (*ddd*, $^3J = 10$, $^4J = 1.2$, 0.7, H−C(2)). ^{13}C-NMR ($CDCl_3$, 62.9 MHz): −4.73, −4.56 (Me_2Si); 18.0 (Me_3CSi); 25.89 (Me_3CSi); 55.77 (MeO); 71.34, 73.60 (C(4), C(6)); 76.83 (C(5)); 97.27 (C(7)); 97.47 (OCH_2O); 116.73 (CN); 127.1 (C(2)); 134.93 (C(3)); 155.75 (C(1)). Anal. calc. for $C_{16}H_{27}NO_4Si$ (325.48): C 59.04, H 8.36, N 4.30; found: C 58.87, H 8.51, N 4.04.

b) *Photoisomerization of* (−)-**15′** into (+)-**15**. In a disk-shaped (diameter *ca.* 63 mm, thickness 11 mm) quartz flask, a soln. of the (*Z*)-isomer (−)-**15′** (123 mg, 0.38 mmol) in dioxane (30 ml) was irradiated with a *Philips-HPK-125* medium-pressure Hg lamp (HPLC monitoring after each 90-s irradiation period: *Zorbax-ODS*, 250 × 4.6 mm; 2.3 ml/min, MeOH/H_2O 85:15; t_R 8 ((−)-**15′**) and 10 min ((+)-**15**); detection at 254 nm). After globally 10.5 min of irradiation, **15**/**15′** *ca.* 1:2 was obtained. The irradiation was stopped, the solvent evaporated, and the resulting oil purified by CC (silica gel, AcOEt/petroleum ether 15:85): successively 38.2 mg (31%) of (+)-**15** and 68 mg (55%) of (−)-**15′**. This experiment was repeated three times, each time with the recovered (*Z*)-isomer (−)-**15′** from the previous run. Thus a total of 73.3 mg (60%) of (+)-**15** (*E*) and 19 mg (15%) of (−)-**15′** (*Z*) were isolated.

*(+)-(2*E*)-{(4*R*,5*S*,6*S*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-(methoxymethoxy)-6-[(2,3,4,6-tetra-*O*-isobutyryl-β-*D*-glucopyranosyl)oxy]cyclohex-2-en-1-ylidene}acetonitrile* (**16**). To a stirred suspension of AgOTf (266 mg, 1.04 mmol) in 1,2-dichloroethane (3 ml) at 20°, protected from light, activated 4-Å molecular sieves (500 mg, powder), 2,6-di(*tert*-butyl)-4-methylpyridine (143 mg, 0.69 mmol, crystals), a soln. of aglycone (+)-**15** (170 mg, 0.52 mmol) in anh. 1,2-dichloroethane (0.5 ml), and the glucosyl bromide **10** (541 mg, 1.03 mmol, crystals) were successively added under a stream of Ar. Then, a soln. of additional 2,6-di(*tert*-butyl)-4-methylpyridine (72 mg, 0.35 mmol) in 1,2-dichloroethane (2.5 ml) was added at the rate of 80 µl/min at 20°, after what the mixture was left for 14 h under stirring. After filtration over *Celite*® and washing of the *Celite*® with CH_2Cl_2 (20 ml), the combined filtrate was evaporated and the residue purified by CC (silica gel, AcOEt/petroleum ether 1:9): **16** (288 mg, 72%). Colorless oil. $[\alpha]_D^{25} = +20.44$ ($c = 3.2$, $CHCl_3$). UV (MeCN): 256.5 (15000). IR (film): 2975, 2937, 2215, 1754, 1471, 1388, 1372, 1346, 1250, 1187, 1145, 1097, 1069, 1045. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.01, 0.12 (2*s*, Me_2Si); 0.93 (*s*, *t*BuSi); 1.07–1.17 (*m*, 4 Me_2CH); 2.43–2.60 (*m*, 4 Me_2CH); 3.39 (*s*, MeO); 3.67 (*ddd*, $^3J = 9.7$, 3.2, 2, H−C(5′)); 3.81 (*dd*, $^3J = 9.6$, 7.4, H−C(5)); 4.07–4.11 (*m*, 1 H−C(6′), H−C(4)); 4.20 (*dd*, $^2J = 12.3$, $^3J = 2$, 1 H−C(6′)); 4.53 (br. *d*, $^3J = 9.6$, H−C(6)); 4.72 (*AB*, $^2J = 6.9$, $\nu_o\delta = 15.3$, OCH_2O); 5.10 ('*d*', $^3J = 7.9$, H−C(1′)); 5.11 ('*dd*', $^3J = 9.1$, 7.9, H−C(2′)); 5.13 ('*dd*', $^3J = 9.7$, 9.1, H−C(4′)); 5.23 (*t*, $^3J = 9.1$, H−C(3′)); 5.56 (br. *s*, C=CHCN); 6.18 (br. *d*, $^3J = 10$, H−C(2)); 6.60 (br. *d*, $^3J = 10$, H−C(3)). ^{13}C-NMR ($CDCl_3$, 100.57 MHz): −4.04, −3.96 (Me_2Si); 18.09, 18.39, 18.69, 18.74, 18.83, 18.99, 19.36 (4 Me_2CH, Me_3CSi); 26.09 (Me_3CSi); 33.80, 33.82, 33.88 (4 Me_2CH); 55.72 (MeO); 61.42 (C(6′)); 68.20 (C(4′)); 71.60 (C(2′)); 72.20 (C(5′)); 72.48 (C(3′)); 74.84 C(6)); 76.33 (C(5)); 81.32 (C(4)); 95.24 (C=*C*HCN); 98.44 (OCH_2O); 99.10

(C(1′)); 116.64 (CN); 124.36 (C(3)); 136.95 (C(2)); 155.54 (C(1)); 175.28, 175.42, 175.89, 176.53 (4 CO). Anal. calc. for $C_{38}H_{61}NO_{13}Si$ (767.98): C 59.43, H 8.01, N 1.82; found: C 59.67, H 8.07, N 1.92.

*(−)-(2*E*)-{(4*R*,5*S*,6*S*)-4,5-Diacetoxy-6-[(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)oxy]cyclohex-2-en-1-ylidene}acetonitrile* (**17**). At 0°, $BF_3 \cdot Et_2O$ (0.5 ml, 4 mmol) was added dropwise to a soln. of **16** (150 mg, 0.195 mmol) in Me_2S (14 ml, 191 mmol). After stirring for 30 min at 0°, the cooling bath was removed. After 24 h at 20°, sat. aq. $NaHCO_3$ soln. (20 ml) was added and the mixture extracted twice with AcOEt (30 ml). The org. phase was washed with a sat. aq. NaCl soln. (20 ml), dried ($MgSO_4$), and evaporated to give an oily residue (135 mg). To a stirred soln. of this oil in anh. MeOH (12 ml), 1M MeONa in MeOH (1 ml, 1 mmol) was added at 0° under Ar. The cooling bath was removed and, after stirring during 1 h at 20°, sufficient *Amberlite® IRC-50* was added to bring the pH to neutrality. MeOH (10 ml) was added, the mixture filtered, the *Amberlite® IRC-50* washed with additional MeOH (20 ml), and the combined filtrate was evaporated. The resulting oil was then acetylated in pyridine/Ac_2O 2:5 (7 ml) during 3 h at 20°. After evaporation at 1 Torr, the residue was directly purified by CC (silica gel, AcOEt/petroleum ether 1:1): **17** (90 mg, 79%). Colorless crystals. M.p. 165–167°. $[\alpha]_D^{25} = -45$ ($c = 0.5$, $CHCl_3$). UV (MeCN): 252 (22100). IR (KBr): 2961, 2940, 2219, 1750, 1742, 1433, 1375, 1316, 1312, 1249, 1242, 1229, 1088, 1068, 1045, 964, 785. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.00, 2.02, 2.03, 2.07, 2.10, 2.14 (6*s*, 6 MeCO); 3.70 (*ddd*, $^3J = 9.5$, 4.4, 2.5, H–C(5′)); 4.14 (*dd*, $^2J = 12.4$, $^3J = 2.5$, 1 H–C(6′)); 4.21 (*dd*, $^2J = 12.4$, $^3J = 4.4$, 1 H–C(6′)); 4.52 (*dd*, $^3J = 10.8$, $^4J = 2$, H–C(6)); 4.76 (*d*, $^3J = 8$, H–C(1′)); 5.07 ('*dd*', $^3J = 9.2$, 8, H–C(2′)); 5.12 ('*dd*', $^3J = 9.5$, 9.2, H–C(4′)); 5.17 (*t*, $^3J = 9.2$, H–C(3′)); 5.26 (*dd*, $^3J = 10.8$, 8.5, H–C(5)); 5.68 (br. *d*, $^3J = 8.5$, H–C(4)); 5.73 (br. *s*, C=CHCN); 5.96 (br. *d*, $^3J = 10.2$, H–C(2)); 6.72 (*dd*, $^3J = 10.2$, 2.1, H–C(3)). ^{13}C-NMR ($CDCl_3$, 100.57 MHz): 20.26, 20.55, 20.56, 20.70, 20.76, 20.94 (6 *Me*CO); 61.36 (C(6′)); 68.07 (C(4′)); 70.70 (C(2′)); 71.30 (C(4)); 72.10 (C(5′)); 72.56 (C(3′)); 73.78 (C(5)); 75.33 (C(6)); 97.55 (C=*C*HCN); 100.89 (C(1′)); 115.88 (CN); 125.65 (C(3)); 133.33 (C(2)); 152.45 (C(1)); 169.21, 169.27, 169.43, 170.30, 170.33, 170.54 (6 Me*C*O). Anal. calc. for $C_{26}H_{31}NO_{14}$ (581.52): C 53.70, H 5.37, N 2.41; found: C 54.14, H 5.57, N 2.60.

*(−)-(2*Z*)-{(4*R*,5*S*,6*S*)-4,5-Diacetoxy-6-[(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)oxy]cyclohex-2-en-1-ylidene}acetonitrile* (*=(−)-Lithospermoside Hexaacetate*; **17′**). As described for (−)-**15′** → (+)-**15**, **17** (80 mg, 0.137 mmol) in dioxane (30 ml) was irradiated and the reaction monitored by HPLC (*Zorbax-Sil*, 250 × 4.6 mm; 1.8 ml/min, AcOEt/hexane 1:1; t_R 12 (**17**) and 15 min (**17′**). After a total of 10 min of irradiation, **17**/**17′** 2:1 was obtained. The irradiation was stopped, the solvent evaporated, and the resulting oil purified by CC (silica gel, AcOEt/petroleum ether 1:1): successively 47.7 mg (60%) of **17**/**17′** 96:4 and 19.2 mg (24%) of **17′**. This experiment was repeated 4 times, each time with the recovered **17**/**17′** mixture from the previous run. A total of 11.2 mg (14%) of **17** was recovered, and 41 mg (51%) of **17′** was obtained as a syrup, which gave white crystals on standing. M.p. 100–104° (dec.) ([3]: 99–100°; [2b]: clear syrup). $[\alpha]_D^{25} = -100$ ($c = 0.7$, $CHCl_3$) ([3]: $[\alpha]_D^{24} = -112.75$ ($c = 1.5$, $CHCl_3$); [4]: $[\alpha]_D^{22} = -108$ ($c = 1.35$, $CHCl_3$)). UV (MeCN): 256.5 (29000) ([3]: 258 (15500, MeOH); [4]: 252 (30000)). IR (KBr): 2962, 2926, 2217, 1755, 1376, 1238, 1052, 1041. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.00, 2.03, 2.05, 2.09, 2.10, 2.11 (6*s*, 6 MeCO); 3.74 (*ddd*, $^3J = 7.1$, 3.4, 2.4, H–C(5′)); 4.11 (*dd*, $^2J = 12.3$, $^3J = 3.4$, 1 H–C(6′)); 4.36 (*dd*, $^2J = 12.3$, $^3J = 2.4$, 1 H–C(6′)); 4.70 (*dd*, $^3J = 7.9$, $^4J = 1.3$, H–C(6)); 4.87 (*d*, $^3J = 7.6$, H–C(1′)); 5.13–5.25 (*m*, H–C(2′), H–C(3′), H–C(4′)); 5.26 (*dd*, $^3J = 7.9$, 5.8, H–C(5)); 5.42–5.46 (*m*, H–C(4), C=CHCN); 5.98 (*dd*, $^3J = 10$, 3.6, H–C(3)); 6.30 (br. *d*, $^3J = 10$, H–C(2)). ^{13}C-NMR ($CDCl_3$, 100.57 MHz): 20.48, 20.61, 20.62, 20.74, 20.85, 20.88 (6 *Me*CO); 61.32 (C(6′)); 68.15 (C(4′)); 68.97 (C(4)); 70.66 (C(2′)); 71.67 (C(5)); 72.19 (C(5′)); 72.77 (C(3′)); 73.99 (C(6)); 100.33 (C=*C*HCN); 101.88 (C(1′)); 115.68 (CN); 128.77 (C(2)); 131.35 (C(3)); 150.76 (C(1)); 169.05, 169.22, 169.31, 170.40, 170.72, 174.15 (6 Me*C*O). Anal. calc. for $C_{26}H_{31}NO_{14}$ (581.52): C 53.70, H 5.37, N 2.41; found: C 53.46, H 5.80, N 2.41.

*(−)-(2*Z*)-{(4*R*,5*S*,6*S*)-6-(β-*D*-Glucopyranosyloxy)-4,5-dihydroxycyclohex-2-en-1-ylidene}acetonitrile* (*=(−)-Lithospermoside*; **1**). At 0°, 1M MeONa in MeOH (0.16 ml, 0.16 mmol) was added to a stirred soln. of **17′** (14 mg, 0.024 mmol) in MeOH (2 ml) under Ar. After 1 h at 0°, sufficient *Amberlite® IRC-50* (*ca.* 0.4 g; previously washed with MeOH) was added to bring the pH to neutrality. MeOH (3 ml) was added, the mixture filtered, the *Amberlite® IRC-50* washed with additional MeOH (7 ml), and the combined filtrate concentrated to *ca.* 0.3 ml. To remove polar impurities, this soln. was purified by filtration over silica gel (0.3 g). Elution with MeOH/AcOEt 2:8 afforded, after evaporation, a white solid, which was recrystallized from aq. MeOH/AcOEt: **1** (7.4 mg, 93%). White crystals. M.p. 271° (dec.) ([2b]: 278–279°; [3]: 263–265° (dec.); [4]: 272–274° (dec.); [5a]: 280° (dec.)). $[\alpha]_D^{25} = -148$ ($c = 0.15$, H_2O) ([2b]: $[\alpha]_D^{20} = -156$ ($c = 0.99$, H_2O); [3]: $[\alpha]_D^{22} = -149$ (H_2O); [4]: $[\alpha]_D^{27} = -138$ ($c = 0.5$, H_2O); [5a]: $[\alpha]_D^{22} = -148$ (H_2O)). UV (H_2O): 258.5 (20000) ([2b]: 260 (21000); [3]: 262 (31000, MeOH); [4]: 259 (15000)). ^{1}H-NMR (D_2O, 400 MHz; calibration of HOD at δ 4.79): 3.4–3.6 (*m*, H–C(2′), H–C(3′), H–C(4′), H–C(5′)); 3.77 (*dd*, $^2J = 12.3$, $^3J = 5.2$, 1 H–C(6′)); 3.95 (*dd*, $^2J = 12.3$, $^3J = 2.1$, 1 H–C(6′)); 3.99 (*dd*, $^3J = 8.3$, 6.1, H–C(5)); 4.33 (*m*, H–C(4)); 4.89 (*dd*, $^3J = 8.3$, $^4J = 1.6$, H–C(6)); 4.92

(*X* of *ABX*, H–C(1′)); 5.67 (br. *s*, C=CHCN); 6.16 (*dd*, ^3J = 10, 3.2, H–C(3)); 6.38 (*dd*, ^3J = 10, ^4J = 1.2, H–C(2)). ^{13}C-NMR (D_2O, 100.57 MHz; calibration of C(1) at δ 157.6 according to [4]): 63.13 (C(6′)); 71.97 (C(Glc)); 72.21 (C(4)); 75.05 (C(Glc)); 76.19 (C(5)); 78.05 (C(6)); 78.15, 78.40 (2 C(Glc)); 99.40 (C=*C*HCN); 104.83 (C(1′)); 119.99 (CN); 129.28 (C(2)); 138.43 (C(3)); 157.60 (C(1)).

2. *Unsuccessful Synthetic Route with Two* ^{t}*BuMe*$_2$*Si Protecting Groups. (±)-(1*RS,*4*RS,*5*SR,*6*SR*)*-5*-exo,*6*-endo-*Dihydroxy-7-oxabicyclo[2.2.1]heptan-2-one* ((±)-**4**). Prepared from (±)-**3** (2 g, 8.54 mmol) according to [9b]: Colorless crystals (1.04 g, 85%) ([9b]: 83%). M.p. 115–116° ([9b]: 112–114°).

*(±)-(1*RS,*4*RS,*5*RS,*6*RS*)*-5*-exo,*6*-endo-*Bis{[(*tert*-*butyl)dimethylsilyl]oxy}-7-oxabicyclo[2.2.1]heptan-2-one* ((±)-**5**). Prepared from (±)-**4** (1.34 g, 9.3 mmol) according to [9b]: Colorless crystals (3.35 g, 96%) ([9b]: 94%). M.p. 46–48° ([9b]: 47.5–49.5°).

*(±)-(2*E*)- and (±)-(2*Z*)-{(1*RS,*4*SR,*5*SR,*6*SR*)*-5*-exo,*6*-endo-*Bis{[(*tert*-*butyl)dimethylsilyl]oxy}-7-oxabicyclo[2.2.1]hept-2-ylidene}acetonitrile* (±)-**6** and (±)-**6′**, resp.). As described for (–)-**14**/(+)-**14′**, with THF (5 ml), KH (670 mg, 16.7 mmol), $(EtO)_2P(O)CH_2CN$ (2.65 ml, 16.8 mmol), and (±)-**5** (3 g, 8.05 mmol) in THF (5 ml) (quenching with sat. aq. $NaHCO_3$ soln. (20 ml)). CC (silica gel, AcOEt/petroleum ether 5:95) gave first (±)-**6** (2.48 g, 78%) and then (±)-**6′** (605 mg, 19%).

*Data of (*E*)-Isomer* (±)-**6**: Colorless crystals. M.p. 96–97°. ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.06, 0.09 (2*s*, 2 Me_2Si); 0.87, 0.91 (2*s*, 2 ^{t}BuSi); 2.45 (br. *d*, ^2J = 17.5, H_{endo}–C(3)); 2.66 (*ddd*, ^2J = 17.5, ^3J = 5.9, ^4J = 2.5, H_{exo}–C(3)); 3.58 (*d*, ^3J = 1.2, H–C(5)); 4.08 (br. *d*, ^3J = 5.2, H–C(6)); 4.39 (br. *d*, ^3J = 5.9, H–C(4)); 4.59 (*d*, ^3J = 5.2, H–C(1)); 5.28 (*m*, C=CHCN).

*Data of (*Z*)-Isomer* (±)-**6′**: Colorless oil. ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.08, 0.13, 0.16 (3*s*, 2 Me_2Si); 0.89–0.91 (2*s*, 2 ^{t}BuSi); 2.35 (*d*, ^2J = 17.5, H_{endo}–C(3)); 2.60 (*dd*, ^2J = 17.5, ^3J = 6.1, H_{exo}–C(3)); 3.60 (br. *s*, H–C(5)); 4.15 (*d*, ^3J = 5.3, H–C(6)); 4.38 (*d*, ^3J = 6.1, H–C(4)); 4.93 (*d*, ^3J = 5.3, H–C(1)); 5.40 (br. *s*, C=CHCN).

*(±)-(2*E*)-{(4*RS,*5*SR,*6*SR*)*-4,6-Bis{[(*tert*-*butyl)dimethylsilyl]oxy}-5-hydroxycyclohex-2-en-1-ylidene}acetonitrile* ((±)-**7**) *and (±)-(2*E*)- and (±)-(2*Z*)-{(4*RS,*5*RS,*6*SR*)*-4,5-Bis{[(*tert*-*butyl)dimethylsilyl]oxy}-6-hydroxycyclohex-2-en-1-ylidene}acetonitrile* ((±)-**8** and (±)-**8′**, resp.). At –30°, 1M $(Me_3Si)_2NLi$ in THF (4.1 ml, 4.1 mmol) was added to a stirred soln. of (±)-**6**/(±)-**6′** (1.4 g, 3.54 mmol) in THF (2 ml) under Ar. After stirring for 20 min at –30°, sat. aq. NH_4Cl soln. (15 ml) and aq. 1M HCl (12 ml) were successively added. The mixture was extracted with AcOEt (75 ml), the org. phase washed with sat. aq. $NaHCO_3$ soln. (20 ml), dried ($MgSO_4$), and evaporated, and the residue purified by CC (silica gel, AcOEt/petroleum ether 1:9): successively (±)-**7** (530 mg, 38%), (±)-**8** (139.5 mg, 10%), and (±)-**8′** (376 mg, 27%) as white solids.

Data of Positional Isomer (±)-**7**: M.p. 94–96°. ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.11, 0.18 (2*s*, 2 Me_2Si); 0.82, 0.96 (2*s*, 2 ^{t}BuSi); 2.32 (*d*, ^3J = 2.4, OH–C(5)); 3.50 (*ddd*, ^3J = 10.3, 7.6, 2.4, H–C(5)); 4,16 (*dd*, ^3J = 10.3, 2.2, H–C(4)); 4.30 (br. *d*, ^3J = 7.6, H–C(6)); 5.44 (br. *s* , C=CHCN); 5.96 (*dd*, ^3J = 10.1, ^4J = 1.3, H–C(2)); 6.56 (*dd*, ^3J = 10.1, 2.2, H–C(3)).

*Data of (*E*)-Isomer* (±)-**8**: M.p. 84–86°. ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.11, 0.15 (2*s*, 2 Me_2Si); 0.90, 0.92 (2*s*, 2 ^{t}BuSi); 3.05 (*d*, ^3J = 5.1, OH–C(6)); 3.70 (*dd*, ^3J = 8, 6.1, H–C(5)); 4.11 (*m*, H–C(6)); 4.24 (*m*, H–C(4)); 5.47 (br. *s*, C=CHCN); 6.04 (br. *d*, ^3J = 10.2, H–C(2)); 6.61 (*dd*, ^3J = 10.2, 1.8 = 1, H–C(3)).

*Data of (*Z*)-Isomer* (±)-**8′**: M.p. 80–81°. ^{1}H-NMR ($CDCl_3$, 250 MHz): 0.09, 0.12, 0.13, 0.15 (4*s*, 2 Me_2Si); 0.83, 0.89 (2*s*, 2 ^{t}BuSi); 4.05–4.09 (*m*, OH–C(6), H–C(4), H–C(5)); 4.56 (*m*, H–C(6)); 5.34 (br. *s*, C=CHCN); 6.04 (*dd*, ^3J = 10, 5, H–C(3)); 6.24 (*d*, ^3J = 10, H–C(2)).

*(±)-(2*E*)-{(4*RS,*5*RS,*6*SR*)*-4,5-Bis{[(*tert*-*butyl)dimethylsilyl]oxy}-6-hydroxycyclohex-2-en-1-ylidene}acetonitrile* ((±)-**8**). Me_3SiOTf (130 µl, 0.72 mmol) and 0.5M $(Me_3Si)_2NK$ in toluene (1.9 ml, 0.95 mmol) were successively added to a stirred soln. of (±)-**6**/(±)-**6′** (100 mg, 0.25 mmol) in THF (2 ml) at 4° under Ar. After stirring at 4° for 6 min, sat. aq. NH_4Cl soln. (5 ml) and aq. 1M HCl (3 ml) were successively added, and the mixture was extracted twice with AcOEt (25 ml). The org. phase was washed with a sat. aq. $NaHCO_3$ soln. (5 ml), dried ($MgSO_4$), and evaporated. AcOH (5 ml) and H_2O (1.7 ml) were added to a soln. of the resulting oil in THF (10 ml). After stirring for 2 h at 20°, sufficient sat. aq. K_2CO_3 soln. was slowly added to neutralization and the mixture extracted twice with AcOEt (20 ml). The org. phase was dried ($MgSO_4$) and evaporated and the residue purified by CC (silica gel, AcOEt/petroleum ether 1:9): (±)-**8** (61 mg, 61%).

*(2*E*)-{(4*R,*5*S,*6*S*)*-4,6-Bis{[(*tert*-*butyl)dimethylsilyl]oxy}-5-[(2,3,4,6-tetra*-O-*isobutyryl-β-*D*-glucopyranosyl)oxy]cyclohex-2-en-1-ylidene}acetonitrile and (2*E*)-{(4*S,*5*R,*6*R*)*-4,6-Bis{[(*tert*-*butyl)dimethylsilyl]oxy}-5-[(2,3,4,6-tetra*-O-*isobutyryl-β-*D*-glucopyranosyl)oxy]cyclohex-2-en-1-ylidene}acetonitrile* (**9** and **9′**). As described for **16**, with AgOTf (198 mg, 0.77 mmol), 1,2-dichloroethane (3 ml), 4-Å molecular sieves (500 mg, powder), 2,6-di(*tert*-butyl)-4-methylpyridine (105 mg, 0.51 mmol, crystals), aglycone (±)-**7** (150 mg, 0.38 mmol, crystals), glycosyl bromide **10** (405 mg, 0.77 mmol, crystals), and additional 2,6-di(*tert*-butyl)-4-methylpyridine (55 mg, 0.27 mmol) in 1,2-dichloroethane (2.5 ml). CC (silica gel, AcOEt/petroleum ether 1:9) yielded

successively diastereoisomers **A** (140 mg) and **B** (135 mg) as colorless syrups of moderate purities which, after crystallization in MeOH/H_2O, afforded pure **A** (112 mg, 35%) and pure **B** (97 mg, 31%) as white crystals.

Data of Diastereoisomer **A** *(***9** or **9′***):* M.p. 119–121°. $[\alpha]_D^{25} = -29.3$ ($c = 1.1$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.03, 0.10, 0.15, 0.22 (4*s*, 2 Me_2Si); 0.94, 0.96 (2*s*, 2 ^{t}BuSi); 1.00–1.23 (*m* 4 *Me*$_2$CH); 2.40–2.60 (*m*, 4 Me_2CH); 3.60 (*ddd*, $^3J = 9.8$, 5.4, 1.7, H–C(5′)); 3.88 (*dd*, $^3J = 10$, 7.2, H–C(5)); 4.08 (*dd*, $^2J = 12$, $^3J =$ 1.7, 1 H–C(6′)); 4.20 (*m*, H–C(6), 1 H–C(6′)); 4.47 (br. *d*, $^3J = 7.2$, H–C(4)); 5.04 (‘*dd*′, $^3J = 9.8$, 9.5, H–C(4′)); 5.05 (‘*dd*′, $^3J = 9.5$, 8.4, H–C(2′)); 5.15 (*t*, $^3J = 9.5$, H–C(3′)); 5.25 (*d*, $^3J = 8.4$, H–C(1′)); 5.55 (br. *s*, C=CHCN); 5.91 (br. *d*, $^3J = 10$, H–C(2)); 6.59 (br. *d*, $^3J = 10$, H–C(3)). ^{13}C-NMR ($CDCl_3$, 100.57 MHz): –4.94, –4.19, –4.05, –3.61 (2 Me_2Si); 17.92, 18.27, 18.74, 18.78, 18.88, 18.96, 18.98 (4 *Me*$_2$CH, 2 Me_3CSi); 25.75, 25.85 (2 *Me*$_3$CSi); 33.80, 33.84 (4 Me_2CH); 61.91 (C(6′)); 68.25 (C(4′)); 71.06 (C(6)); 71.09 (C(2′); 72.21 (C(5′)); 72.70 (C(3′)); 75.20 C(4)); 80.79 (C(5)); 93.88 (C=*C*HCN); 99.17 (C(1′)); 116.69 (CN); 123.80 (C(3)); 137.46 (C(2)); 158.54 (C(1)); 175.24, 175.35, 176.04, 176.65 (4 CO).

Data of Diastereoisomer **B** *(***9** or **9′***):* M.p. 89–91°. $[\alpha]_D^{25} = +21.9$ ($c = 0.46$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.05, 0.09, 0.15, 0.25 (4*s*, 2 Me_2Si); 0.8–1.2 (*m*, 2 ^{t}BuSi, 4 *Me*$_2$CH); 2.38–2.57 (*m*, 4 Me_2CH); 3.63 (*ddd*, $^3J = 9.7$, 5.4, 2.1, H–C(5′)); 4.07 (*dd*, $^3J = 10.1$, 7.4, H–C(5)); 4.08–4.15 (*m*, CH_2(6′)); 4.28 (br. *d*, $^3J = 10.1$, H–C(6)); 4.33 (br. *d*, $^3J = 7.4$, H–C(4)); 5.00–5.08 (*m*, H–C(2′), H–C(3′), H–C(4′)); 5.17 (*d*, $^3J = 8.1$, H–C(1′)); 5.38 (br. *s*, C=CHCN); 5.96 (br. *d*, $^3J = 10.2$, H–C(2)); 6.54 (*dd*, $^3J = 10.2$, 1.3, H–C(3)). ^{13}C-NMR ($CDCl_3$, 100.57 MHz): –4.19, –4.05 (2 Me_2Si); 18.07, 18.10, 18.55, 18.67, 18.73, 18.85, 18.86, 19.37 (4 *Me*$_2$CH, 2 Me_3CSi); 25.75, 26.05 (2 *Me*$_3$CSi); 33.70, 33.81, 33.84 (4 Me_2CH); 61.97 (C(6′)); 68.46 (C(4′)); 71.73, 71.74 (C(4), C(2′)); 72.44 (C(5′)); 72.72 (C(3′)); 73.99 (C(6)); 79.11 C(5)); 93.16 (C=*C*HCN); 98.52 (C(1′)); 116.40 (CN); 123.14 (C(3)); 139.19 (C(2)); 159.00 (C(1)); 175.29, 175.36, 175.99, 176.58 (4 CO).

REFERENCES

[1] D. Josien-Lefebvre, C. Le Drian, ‘Journées Grand-Est II, Société Française de Chimie’, March 29–30, 2001, Nancy, France.

[2] a) A. Sosa, C. Sosa-Bourdouil, C. Hardy, *C. R. Acad. Sci.* **1955**, *240*, 1570; b) A. Sosa, F. Winternitz, R. Wylde, A. A. Pavia, *Phytochemistry* **1977**, *16*, 707.

[3] D. Dwuma-Badu, W. H. Watson, E. M. Gopalakrishna, T. U. Okarter, J. E. Knapp, P. L. Schiff, D. J. Slatkin, *Lloydia* **1976**, *39*, 385.

[4] J. Wu, E. H. Fairchild, J. L. Beal, T. Tomimatsu, R. W. Doskotch, *J. Nat. Prod.* **1979**, *42*, 500.

[5] a) V. Plouvier, *Phytochemistry* **1978**, *17*, 1010; b) H. Itoh, T. Hatano, M. Miyake, T. Yoshida, M. Kozuka, H. Tokuda, T. Okuda, in ‘Polyphenols 94’ (Les Colloques, n° 69), INRA Editions, Paris, 1995, p. 419.

[6] C. A. Elliger, A. C. Waiss, R. E. Lundin, *J. Org. Chem*. **1974**, *39*, 2930; K. Takahashi, S. Matsuzawa, M. Takani, *Chem. Pharm. Bull*. **1978**, *26*, 1677; K. Ueda, K. Yasutomi, I. Mori, *Chem. Lett*. **1983**, 149; C. C. Chen, Y. P. Chen, H. Y. Hsu, K. H. Lee, S. Tani, A. T. McPhail, *J. Nat. Prod.* **1985**, *48*, 933; A. Nahrstedt, V. Wray, *Phytochemistry* **1990**, *29*, 3934; T. P. Abbott, L. K. Nakamura, G. Buchholz, W. J. Wolf, D. M. Palmer, H. J. Gasdorf, T. C. Nelsen, R. Kleiman, *J. Agric. Food Chem*. **1991**, *39*, 1488; N. Chida, K. Yamada, S. Ogawa, *J. Chem. Soc., Perkin Trans. 1* **1992**, 1131; T. Nakanishi, M. Nishi, M. Somekawa, H. Murata, M. Mizuno, M. Iinuma, T. Tanaka, J. Murata, F. A. Lang, A. Inada, *Chem. Pharm. Bull*. **1994**, *42*, 2251; A. J. J. Van Den Berg, S. F. A. J. Horsten, J. J. Kettenes-Van Den Bosch, B. H. Kroes, R. P. Labadie, *Phytochemistry* **1995**, *40*, 597; K. Yamasaki, in ‘Advances in Plant Glycosides, Chemistry and Biology’, Eds. C.-R. Yang and O. Tanaka, Elsevier, Amsterdam, 1999, p. 335.

[7] D. Josien-Lefebvre, G. Desmares, C. Le Drian, *Helv. Chim. Acta* **2001**, *84*, 890.

[8] E. Vieira, P. Vogel, *Helv. Chim. Acta* **1983**, *66*, 1865; K. A. Black, P. Vogel, *Helv. Chim. Acta* **1984**, *67*, 1612; A. Warm, P. Vogel, *J. Org. Chem*. **1986**, *51*, 5348; J. L. Reymond, P. Vogel, *Tetrahedron: Asymmetry* **1990**, *1*, 729; A. Forster, T. Kovac, H. Mosimann, P. Renaud, P. Vogel, *Tetrahedron: Asymmetry* **1999**, *10*, 567.

[9] a) C. Le Drian, E. Vieira, P. Vogel, *Helv. Chim. Acta* **1989**, *72*, 338; P. Vogel, D. Fattori, F. Gasparini, C. Le Drian, *Synlett* **1990**, *4*, 173; S. Jeganathan, P. Vogel, *Tetrahedron Lett.* **1990**, *31*, 1717; E. de Guchteneere, D. Fattori, P. Vogel, *Tetrahedron* **1992**, *48*, 10603; O. Arjona, A. de Dios, J. Plumet, B. Saez, *Tetrahedron Lett.* **1995**, *36*, 1319; O. Arjona, A. de Dios, J. Plumet, B. Saez, *J. Org. Chem.* **1995**, *60*, 4932; J. Cossy, J.-L. Ranaivosata, V. Bellosta, *Tetrahedron* **1996**, *52*, 629; N. Jotterand, P. Vogel, *Synlett* **1998**, 1237; P. Renaut, J. Millet, C. Sepulchre, J. Theveniaux, V. Barberousse, V. Jeanneret, P. Vogel, *Helv. Chim. Acta* **1998**, *81*, 2043; A. Forster, J. Fitremann, P. Renaud, *Tetrahedron Lett.* **1998**, *39*, 3485; A. Forster, J. Fitremann, P. Renaud, *Tetrahedron Lett.* **1998**, *39*, 7097; b) C. Le Drian, J. P. Vionnet, P. Vogel, *Helv. Chim. Acta* **1990**, *73*, 161.

[10] G. Desmares, D. Lefebvre, G. Renevret, C. Le Drian, *Helv. Chim. Acta* **2001**, *84*, 880.
[11] C. Le Drian, P. Vogel, *Helv. Chim. Acta* **1987**, *70*, 1703.
[12] a) K.-H. Chung, H. G. Lee, I.-Y. Choi, J.-R. Choi, *J. Org. Chem.* **2001**, *66*, 5937; b) D. B. Berkowitz, S. Choi, J.-H. Maeng, *J. Org. Chem.* **2000**, *56*, 847; c) M. Kawanisi, Y. Itoh, T. Hieda, S. Kozima, T. Hitomi, K. Kobayashi, *Chem. Lett.* **1985**, 647; R. Cacciapaglia, L. Mandolini, *J. Org. Chem.* **1988**, *63*, 2579.
[13] K. Fuji, S. Nakano, E. Fujita, *Synthesis* **1975**, 276.
[14] S. Sugiyama, M. Honda, R. Higuchi, T. Komori, *Liebigs Ann. Chem.* **1991**, 349; D. R. Kelly, S. M. Roberts, R. F. Newton, *Synth. Commun.* **1979**, *9*, 295.
[15] D. D. Perrin, W. L. F. Armarego, 'Purification of Laboratory Chemicals', 3rd edn., Pergamon Press, Oxford, 1988.

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