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A FACILE SYNTHESIS OF 7,9-DI-(*p*-METHOXYBENZYL)-7,9-DIAZA-5-METHYLENE-6-(*t*-BUTYLDIMETHYLSILYL)OXY-2-OXABICYCLO[4,2,2]DECANE-8,10-DIONE

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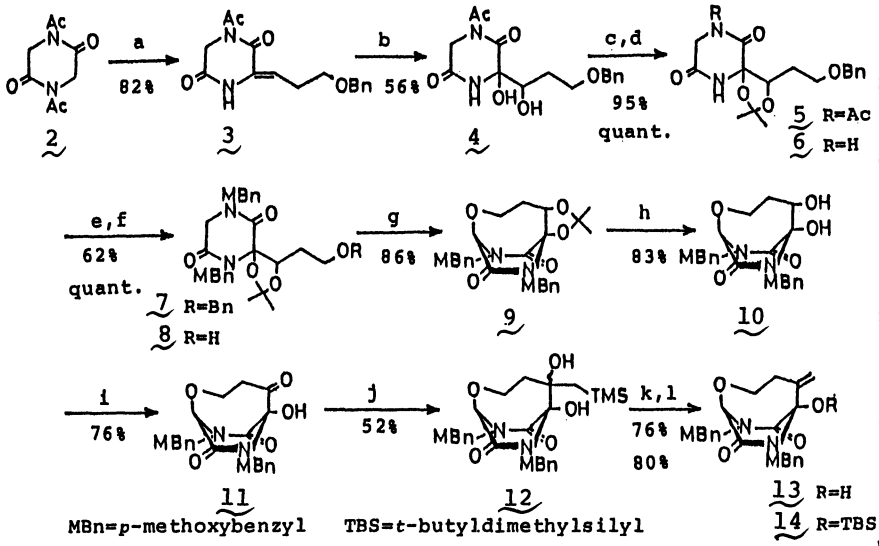
The title compound, a key intermediate for a total synthesis of bicyclomycin, was obtained from *N,N'*-diacetyl-anhydroglycine through 12 steps in ca. 4% overall yield.

On bicyclomycin[1] (1) the synthesis of racemic compound[2] and its desmethylene derivative[3] have been reported. For an elegant synthesis of optically active 1, it was considered necessary to overcome three difficult problems. The easiest first problem was the selection of chiral source, and we prepared 2-*C*-methyl-L-glyceraldehyde from 3-*C*-methyl-D-glucose derivatives by descending method for the three-carbon branch of 1.[4] The second problem involved developing a suitable *N*-blocking and its de-blocking method under mild conditions, and we reported that *N*-*p*-methoxybenzyl group can be easily removed by ammonium cerium nitrate.[5] The third was a facile construction of the bicyclic skeleton of 1, especially the introduction of *exo*-methylene function, and this report communicates the synthesis of the racemic skeleton. As shown in Scheme 1, condensation of *N,N'*-diacetyl-anhydroglycin (2) with 3-benzyloxypropanal gave selectively the (1z)-alkylidene derivative (3; mp 119 °C), having three-carbon unit for bicyclic system formation. Oxidation of the olefinic function of 3 gave the diol (4: mp 92 °C), furnishing a necessary tertiary hydroxy group and a secondary one for introduction of methylene function. The diol function was protected with isopropyridene group (5: mp 151 °C and 138-140 °C),[6] and then remaining *N*-acetyl group was removed (6: mp 164 °C). The two amido groups of 6 were protected with *p*-methoxybenzyl group (7: mp 131 °C), and then *O*-benzyl group was selectively hydrogenolyzed (8: mp 159 °C). Now, cyclization of 8 could be achieved by treatment with NBS and $BaCO_3$[7] to give bicyclic 9 (mp 168 °C). *O*-Deisopropylidenation of 9 gave the diol 10 (mp 154-155 °C), and then secondary hydroxy group was selectively oxidized into a ketone function (11: mp 138 °C). Introduction of methylene function was accomplished by successive reaction with $TMSCH_2MgCl$ (12: sirup)[8] and an improved Peterson elimination[9] (13: sirup). Conventional *t*-butyldimethylsilylation of 13 gave the title compound [14: hard sirup, NMR data ($CDCl_3$) of the skeleton: ^1H: δ 5.08s (H-1),

3.8-3.5m and 3.4-3.2m (2H, H-3a, 3b), 2.4-1.6m (2H, H-4a, 4b), 5.47s and 4.96s (2H, $=CH_2$); ^{13}C (ppm): 81.5d (C-1), 63.8t (C-3), 35.7t (C-4), 148.6s (C-5), 87.9s (C-6), 167.6s and 163.4s (C-8, 10), 118.0t ($=CH_2$)] which is ready for condensation with a chiral three-carbon unit mentioned above.



Reagents and conditions: a) 1.3 equiv. 3-benzyloxypropanal, 1.05 equiv. 0.5 M *t*-BuOK/*t*-BuOH, DMF, r.t., 12 h; b) 5 equiv. $NaClO_3$-cat. amount OsO_4, dioxane-water (4:1), r.t., 3 d; c) 7 equiv. 2-methoxypropene, cat. pyridinium *p*-toluenesulfonate, acetone, r.t., 3 d; d) 3 equiv. $H_2N\text{-}NH_2\cdot H_2O$, DMF 0 °C, 3 h; e) 2.1 equiv. NaH, 2.2 equiv. MBnBr, DMF, r.t., 12 h; f) 10% Pd/C-H_2, MeOH, 1 d; g) 1.05 equiv. NBS, $BaCO_3$, molecular sieves 4A, $CHCl_3$, r.t., 3 d; h) 2M HCl-THF (2:5), 1 d; i) DMSO, 3 equiv. COCl-COCl, CH_2Cl_2, -78 °C, 20 min, then Et_3N, -78 °C,5 min → r.t.; j) 3 equiv. $TMSCH_2MgCl$, ether-THF, -15 °C → r.t., 6 h; k) *i*) 10 equiv. $(CF_3CO)_2O$, 20 equiv. 4-dimethylaminopyridine, CH_2Cl_2, r.t., 2 h; *ii*) 30 equiv. KF, 15 equiv. *t*-Bu_4NCl, CH_3CN, r.t., 12 h; l) 1.5 equiv. TBS-triflate, 2.0 equiv. 2,6-lutidine, CH_2Cl_2, r.t., 12 h.

Scheme 1.

References

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8) A 1:4 mixture of diastereomers was obtained.

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