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HIGH-PRESSURE (4+2)CYCLOADDITION OF 1-METHOXYBUTA-1,3-DIENE TO α-AMINO ALDEHYDES. INFLUENCE OF *N*-PROTECTING GROUPS ON ASYMMETRIC INDUCTION

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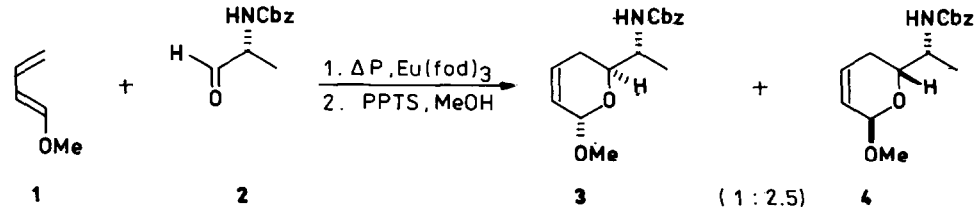
Abstract - The stereochemistry of the high-pressure (4+2)cycloaddition reaction of 1-methoxybuta-1,3-diene with *N*-benzyloxycarbonyl-, *N*-phthaloyl-, and *N*-benzyl-*N*-*tert*-butoxycarbonyl-D-alaninal is discussed, and methyl 2,6-di-*N*-acetyl-α-D-purpurosaminide B is synthesized.

The high-pressure Diels-Alder reaction of buta-1,3-diene derivatives with carbonyl compounds is a convenient method for the preparation of variously substituted 5,6-dihydro-2*H*-pyrans.[1] Special attention has been given to (4+2)cycloaddition with the use of chiral carbonyl heterodienophiles which, in the reaction with 1,3-dienes, afford optically active 6-substituted 5,6-dihydro-2*H*-pyrans.[2,3] The application of optically pure *N*-protected α-amino aldehydes to the Diels-Alder reaction[4,5] offers an easy access to the important components of aminoglycoside antibiotics, which are difficult to obtain by other routes.

There are very few papers concerning stereochemical control in (4+2)cycloaddition to the carbonyl group of α-amino aldehydes.[7-9] Because of relatively poor knowledge and owing to a growing interest in this topic, we resolved to study the influence of the nature of the amine-protecting groups on the stereochemical course of the Diels-Alder reaction with α-amino aldehydes.

The $Eu(fod)_3$-mediated[10] high-pressure (4+2)cycloaddition of 1-methoxybuta-1,3-diene (1) to Cbz-D-alaninal (2), carried out in ethyl ether as solvent under 20 kbar[11] at 50°C, afforded, after acidic isomerisation,[12] a 1:2.5 mixture of two adducts 3 and 4[13] in a 50% overall yield (Scheme 1).

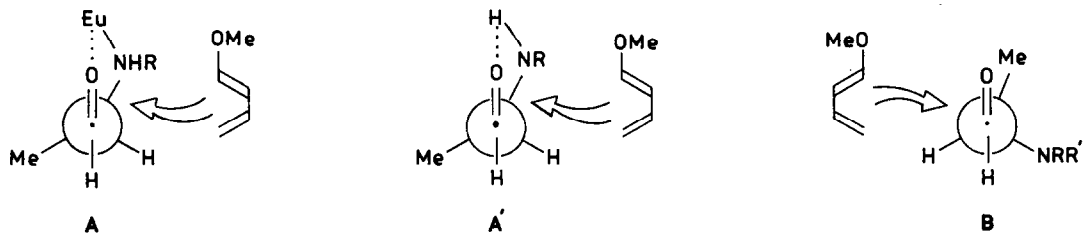


1 2 3 (1 : 2.5) 4

Scheme 1

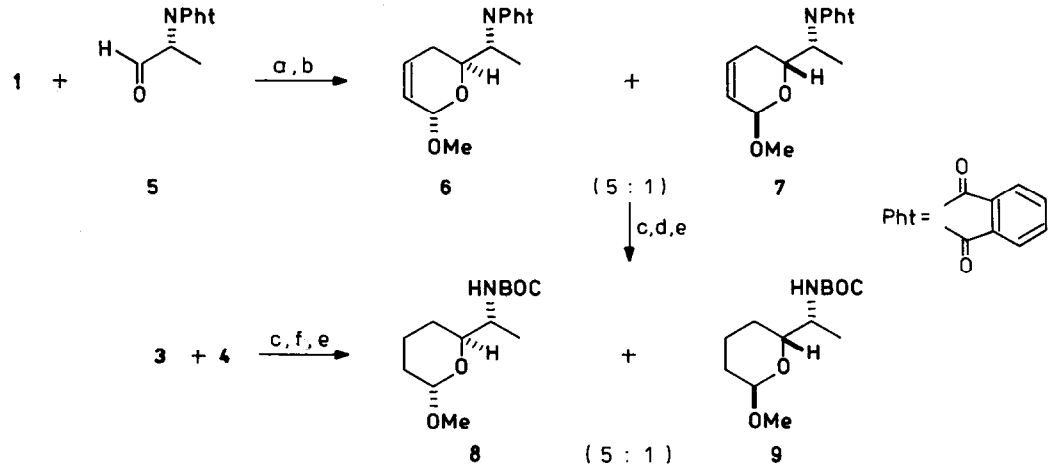
Taking into account the results of the Diels-Alder reaction of diene 1 with 2,3-*O*-isopropylidene-D-glyceraldehyde,[2] and those of the cyclocondensation reaction between Danishefsky's diene and aldehyde derived from L-serine,[7] it seemed that the high-pressure reaction of 1 with 2, carried out without catalyst, should give rise to the 5,6-*anti*-diastereoisomer 3 as

a major product. In fact, the diastereoisomeric ratio was very similar (i.e. *anti*:*syn*=1:2.5) to that obtained from the Lewis acid-catalysed reaction. These results are consistent with the chelation-controlled cycloaddition to conformer A (Scheme 2). The lack of inversion of stereochemistry, in the case of the noncatalysed reaction, can be explained by a hydrogen bonding interaction between the carbonyl group and N*H* proton as shown in conformer A'.



Scheme 2

At this point we resolved to examine a different protection of the amino group which "consumes" both N*H* protons. Indeed, *N*-phthaloyl-D-alaninal (5) reacted with diene 1 under high-pressure conditions to afford, after acidic isomerisation, a 5:1 mixture of adducts 6 and 7[13] in a 75% overall yield (Scheme 3).

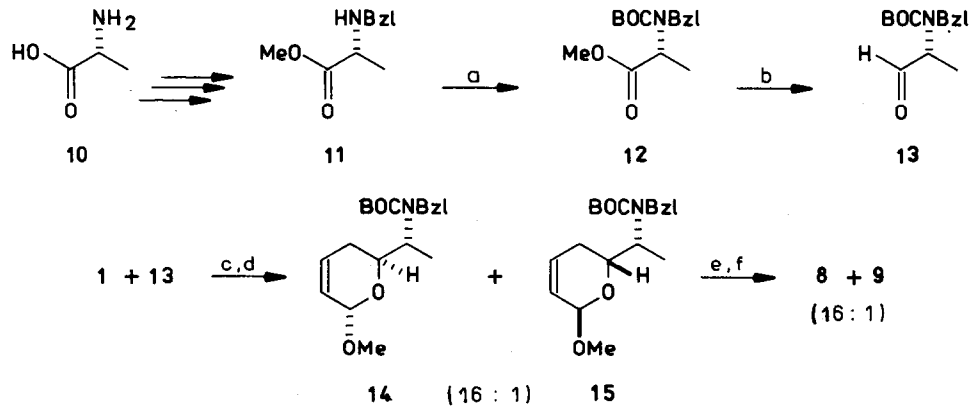


Scheme 3. Reagents and reaction conditions: (a) 15 kbar, 50°C, $Eu(fod)_3$, CH_2Cl_2; (b) PPTS, MeOH, RT; (c) H_2, Pd/C, EtOAc, RT; (d) $N_2H_4 \cdot H_2O$, EtOH, reflux; (e) BOC-ON, EtOAc, RT; (f) Na, NH_3, THF, -33°C.

Chemical correlation of adducts 6 and 7 with adducts 3 and 4 was performed *via* compounds 8 and 9[13,14] as shown in Scheme 3. Reversing the direction of asymmetric induction indicates that in the case of *N*,*N*-diprotected aldehyde conformer B (Scheme 2) predominates.

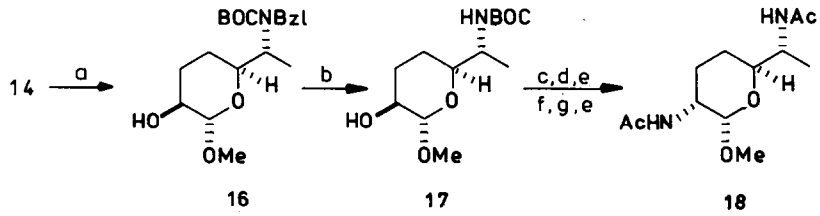
To prove the generality of these findings we decided to test other *N*,*N*-diprotected α-amino aldehydes. Scheme 4 illustrates our attempts to solve this problem. *N*-Benzyl-D-alanine methyl ester (11), obtained from D-alanine (10) using a known procedure,[15] was transformed into *N*-benzyl-*N*-*tert*-butoxycarbonyl methyl ester (12).[16] Reduction of ester 12, followed by flash chromatography, gave pure aldehyde 13 which was immediately subjected to the cycloaddition reaction. The high-pressure (4+2)cycloaddition of diene 1 to aldehyde 13 afforded, after aci-

dic isomerisation, a16:1 mixture of two diastereoisomers 14 and 15[13] in an 80% overall yield. For correlation adducts 14 and 15 were transformed into compounds 8 and 9,[14] respectively, as shown in Scheme 4.



Scheme 4. Reagents and reaction conditions: (a)$(BOC)_2O$, DMAP, MeCN, RT; (b) DIBAL, Et_2O,-78°C; (c) 15 kbar, 50°C, 2% $Eu(fod)_3$, Et_2O; (d) PPTS, MeOH, RT; (e) H_2, Pd/C, EtOAc, RT; (f) Na, NH_3, THF, -33°C.

The final proof of absolute configuration of the major adduct 14 was based on its transformation into methyl 2,6-di-*N*-acetyl-α-D-purpurosaminide B (18) (Scheme 5).[17]



Scheme 5. Reagents and reaction conditions: (a) *i*. $ThxBH_2$, Et_2O, -20°C; *ii*. H_2O_2, NaOH, RT; (b) Na, NH_3, THF, -33°C; (c) PCC, molecular sieves 4Å, CH_2Cl_2, RT; (d) $NH_2OH{\cdot}HCl$, MeOH, RT; (e) Ac_2O, Et_3N, CH_2Cl_2, RT; (f) $BH_3{\cdot}THF$, -78°C→RT; (g) TFA, RT.

A 16:1 mixture of adducts 14 and 15 was subjected to hydroboration using thexyl borane, which, followed by oxidative work-up, afforded in a 70% yield the alcohol 16 contaminated by its diastereoisomer derived from the minor adduct 15. The alcohol 16 was, after chromatographic purification, debenzylated *via* reduction usinf a sodium-liquid ammonia system, to produce the respective alcohol 17. Functionalisation of the latter alcohol was carried out similarly as in our total syntheses of purpurosamine C[18] and 6-*epi* B,[5] to afford methyl 2,6-di-*N*--acetyl-α-D-purpurosaminide B (18) in a 20% overall yield. Analytically pure compound 18 was obtained by recrystallisation from acetone: mp 262-263°C, $[\alpha]_{589}^{20}$ +186° (c 0.5, MeOH); lit.[19] mp 261-262°C, $[\alpha]_{589}^{20}$ +186.5° (c 0.7, MeOH). The ^1H NMR and IR spectra were superimposable on those of an authentic sample.

The above results show that the stereochemistry of (4+2)cycloaddition with α-amino aldehydes as heterodienophiles can be controlled under high-pressure conditions. We demonstrated that there is a great difference between the protecting groups "consuming" either one or two *NH* protons of the amino group. When we used *N*,*N*-diprotected α-amino aldehydes instead of

N-monoprotected, the direction of asymmetric induction was reversed as a result of substantial changes in the nature of the α-amino group protection from steric to chelating character.

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References and Notes

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14. Chromatographic separation afforded the major diastereoisomer 8 (oil, $[\alpha]_{589}^{20}$ -90.5° (c 1.4, $CHCl_3$)), and the minor diastereoisomer 9 (oil, $[\alpha]_{589}^{20}$ +64.7° (c 1.5, $CHCl_3$)).
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