Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3359–3363

TETRAHEDRON:
ASYMMETRY

Cycloaddition reactions of carbohydrate derivatives. Part 7: [3+2] cycloadditions of chiral nitrilimines

Attila Agócs,[a] Attila Bényei,[b,†] László Somogyi[a] and Pál Herczegh[a,*]

[a]*Research Group for Antibiotics of the Hungarian Academy of Sciences, Kossuth Lajos University, PO Box 70, H-4010 Debrecen, Hungary*

[b]*Department of Physical Chemistry, Kossuth Lajos University, H-4010 Debrecen, Hungary*

Received 18 August 1998; accepted 3 September 1998

Abstract

The diastereoselective 1,3-dipolar cycloaddition reactions of chiral alkenes with a nitrilimine derived from D-galactose phenylhydrazone were studied. The best stereoselectivity was observed with *N*-acryloyl-(−)-camphor sultam **9**, as the chiral inductor, to produce compound **8**. © 1998 Elsevier Science Ltd. All rights reserved.

Although nitrilimines represent an intensively studied class of 1,3-dipoles,[1] until very recently no data on their diastereoselective cycloaddition reactions have been reported, and chiral nitrilimines have not been prepared.[2] After completing the present work, the first diastereoselective cycloaddition reaction of an achiral nitrilimine with a chiral dipolarophile was described.[3] When the preparation of this manuscript was finished, a paper on the diastereoselective [3+2] cycloaddition of nitrilimines with Fisher carbene complexes[16] appeared. In continuation of our studies on the cycloaddition reactions of carbohydrates[4] it was decided to study the preparation and investigation of sugar-derived nitrilimines, as potential precursors to the analogs of some important alkaloid antibiotics.

The simplest access to nitrilimines is based on the dehydrohalogenation of hydrazonoyl halides.[5] For the generation of the carbohydrate-derived hydrazonoyl bromide **2**, D-galactose phenylhydrazone penta-*O*-acetate[6] **1** was treated with an excess of *N*-bromosuccinimide and dimethyl sulfide (Corey–Kim reagent[7]) according to the method of Patel et al.[8] (Fig. 1). Dehydrohalogenation of **2** with triethylamine in the presence of methyl acrylate gave the nitrilimine **3**, which was immediately transformed into the 4-bromophenylpyrazoline **4** as a 1:1 mixture of diastereomers, and one of them could be isolated by crystallization from ether/hexane. Compound **4** could also be obtained from the 4-bromophenylhydrazone **10** with the same reaction sequence. Interestingly enough, Patel et al.[8] did not report on the aromatic bromination of the phenylhydrazones of aryl or aralkyl aldehydes when the reagent was employed in excess.

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[*] Corresponding author. E-mail: herczeghp@tigris.klte.hu

[†] OTKA postdoctoral fellow.

PII: S0957-4166(98)00356-5

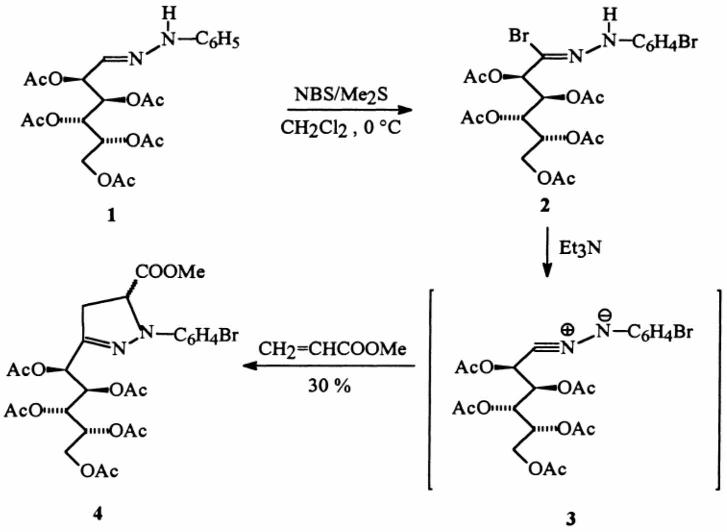


Fig. 1.

We expected to enhance the stereoselectivity of the cycloadditions of **3** with the use of chiral acrylic esters and amides as dipolarophiles[9] (Fig. 3). Thus, reaction with (−)-menthyl acrylate[10] gave an isomeric mixture of **5** (double stereoselection of a mismatching pair of reagents), while the corresponding enantiomer ensured higher diastereoselectivity (**6**, matching pair). With (1*R*)-*endo*-fenchyl acrylate[11] a mixture of isomers (**7**) was also obtained. In the latter three cases, the ratios of diastereoisomers were determined by HPLC.

Contrary to the above results, when the Oppolzer's camphor sultam derivative[12,13] **9** was applied as the chiral inductor, compound **8** was detectable exclusively in the reaction mixture, the structure of the adduct being elucidated by X-ray crystallography[14] (Fig. 2). The observed selectivity of this latter reaction is in good accordance with the model of Kim and Curran for asymmetric nitrone cycloadditions.[15]

As expected, *N*-acryloyl-(+)-camphor sultam had a poorer selectivity (constituting a mismatching pair

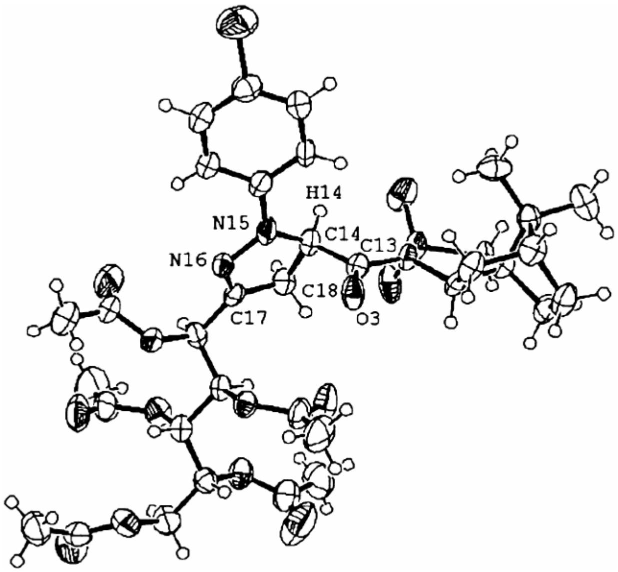


Fig. 2. X-Ray structure of **8**.

with **9**), and in fact two diastereomers **11** were isolated in an 8:2 ratio (Fig. 3). To estimate the extent of chiral induction exerted by the sugar moiety, the achiral benzaldehyde *p*-bromophenylhydrazone **12** was selected as the nitrilimine source (Fig. 4) and a d.e. of 54% **13** was observed. This finding suggests that the contribution of the sugar portion to the stereocontrol is smaller than that of an appropriate chiral inductor built in the alkene reaction partner. It is interesting to note that despite its close structural analogy with the camphor grouping, the fenchyl group is not an efficient inductor at all, as yields for the three- and four-step one-pot reaction sequences leading to the chiral pyrazolines were in the range of 30–40% (60–70% for each step). Further chemical transformations of the cycloadducts are being studied.

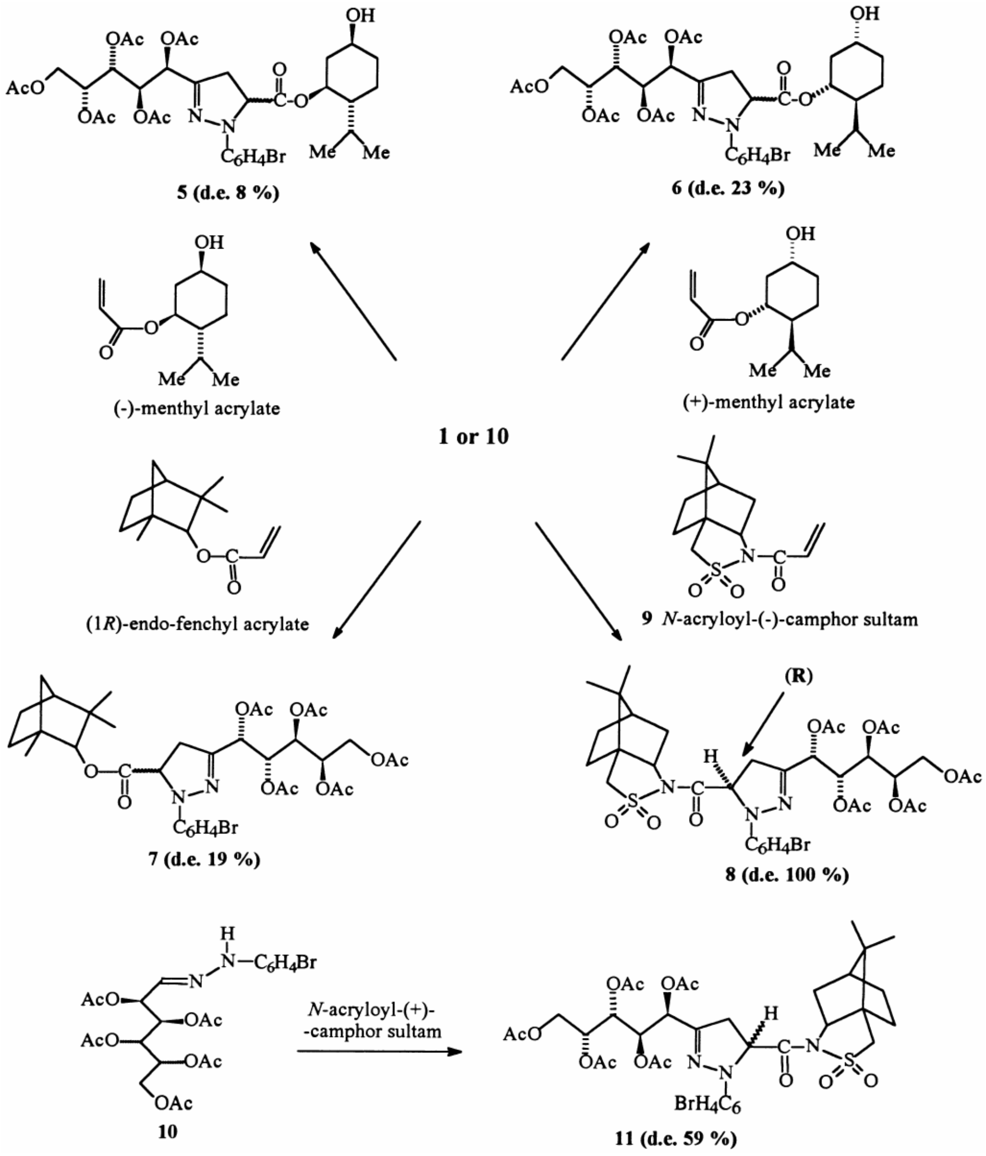
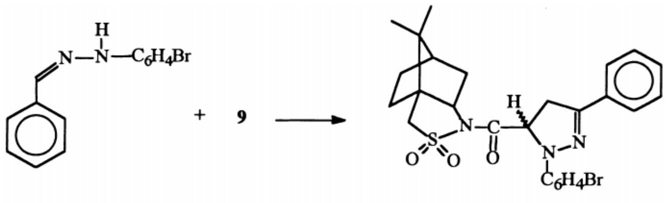


Fig. 3.



12

13 (d.e. 54 %)

Fig. 4.

Acknowledgements

The authors thank the Hungarian Scientific Research Fund for financial support (Grant Nos. T 019338, T 014205 and D 25136), and Mr. Tamás Menyhárt for his skillful technical assistance.

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9. New compounds were characterized by spectroscopic (NMR, MS) methods and/or elemental analysis. Preparation and spectroscopic data for (2*S*)-*N*-[[2-(4-bromophenyl)-5-((1*R*,2*S*,3*S*,4*R*)-1,2,3,4,5-pentaacetoxypentyl)-(3*R*)-3,4-dihydro-2*H*-pyrazole-3-yl]carbonyl]-bornane-2,10-sultam **8**: *N*-bromosuccinimide (NBS, 2.4 g) and dimethyl sulfide (2 ml) were dissolved in dry CH_2Cl_2 at 0°C. Ten minutes later, 3.4 g (1.7 mM) of the *p*-bromophenylhydrazone **10** was added to the yellow suspension at 0°C. One hour later, *N*-acryloyl-(−)-camphor sultam (**9**; 0.7 g) and triethylamine (6 ml) were added to the orange suspension at 0°C. After 30 min the mixture was washed with sat. aq. $NaHCO_3$, dried and evaporated. Column chromatography with hexane:ethyl acetate (6:4) resulted in a reddish syrup, from which 0.65 g (31%) of pure **8** was obtained by crystallization from ethanol. M.p.: 142–143°C; $[\alpha]_D^{23}$ +101.0 (*c* 1.02, $CHCl_3$); PSP-MS m/z 827 $(M+H)^+$; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 1.0 and 1.2 (6H, 2s, 2 methyl), 1.33, 1.44 and 1.9 [7H, 3m, 6, 8, 9 $-CH_2-$ and H-7 ($-CH-$) of sultam], 1.9–2.1 (15H, m, 5 acetyl), 3.08 (1H, dd, H-2b (pyr. ring) $J_{2a,2b}$=18 Hz, $J_{3,2b}$=6 Hz), 3.28 (1H, dd, H-2a, $J_{2a,3}$=12.5 Hz (pyr. ring)), 3.48 and 3.58 (2H, 2d, $-CH_2SO_2-$), 3.9 (1H, dd+dd, N*CH*, (sultam) $J_{5,6a}$=$J_{5,6b}$=6.5 Hz, H-5′b (CH_2 sugar) $J_{4',5'b}$=5.5 Hz, $J_{5'a,5'b}$=11.5 Hz), 4.26 (1H, dd, H-5′a (CH_2 sugar)), 5.24 (1H, ddd, H-4′, $J_{3',4'}$=1.5 Hz), 5.35 (1H, dd, H-3 (pyr. ring)), 5.45 (1H, dd, H-3′, $J_{2',3'}$=9.5 Hz), 5.67 (2H, d+dd, H-1′ and H-2′, $J_{1',2'}$=2.5 Hz), 6.82 and 7.3 (4H, 2d, aromatic J_{ortho}=9 Hz).
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14. Colorless block crystals (0.4×0.2×0.1 mm) of $C_{35}H_{44}BrN_3O_{13}S$, grown from dichloromethane/ether, M=826.7, monoclinic, a=10.230(5) Å, b=14.174(4) Å, c=14.08(1) Å, β=105.81°, V=1964(1) Å^3, Z=2, space group: $P2_1$, ρ_{calc}=1.398 g cm^{-3}. Data were collected at 293(1) K, Enraf–Nonius MACH3 diffractometer, MoKα radiation, λ=0.71073, $\omega-2\theta$ motion, θ_{max}=25.24°, 4022 reflections of which 2927 were unique with $I>2\sigma(I)$, decay: 4%. The structure was solved

using the SIR-92 software (Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Cryst*. 1993, **26**, 343–350) and refined on F^2 using the SHELX-97 program (Sheldrick, G. M. SHELXL-93, Universität Göttingen, Germany, 1993), $R(F)$=0.0466 and $wR(F^2)$=0.0992 for 4022 reflections, 478 parameters, H atoms were fixed, Flack parameter: −0.00(1) (Flack, H. D. *Acta Cryst*. A 1983, **39**, 876–881).

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