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Communications

Hetero-Diels–Alder Reactions on a Carbohydrate Template: Stereoselective Synthesis of (*S*)-Anabasin

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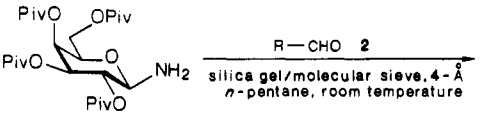
Summary: Diastereoselective aza-Diels–Alder reaction using the tetra-*O*-pivaloyl-β-D-galactopyranosylamine as the chiral template affords the synthesis of enantiomerically pure 2-substituted piperidine derivatives, e.g. the tobacco alkaloid (*S*)-anabasin.

Sir: *O*-Acylglycosylamines, in particular the 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine **1**, proved to be effective chiral templates[1] in Strecker[2] and Ugi syntheses[3] of α-amino acid derivatives. In these processes the aldimines **3** are formed as the intermediates from **1** and the aldehydes **2** (Scheme I).

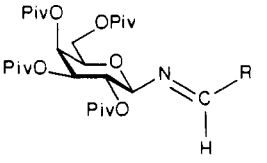
We here report on the use of *N*-galactosyl imines **3** as the dienophiles in diastereoselective hetero-Diels–Alder syntheses,[4] which constitute the first method of this type that allows both the detachment of the chiral piperidine derivatives from the template and the reisolation of the auxiliary. The imines **3**, often prone to anomerization, can be synthesized from **1** and aldehydes **2** in *n*-pentane in the presence of molecular sieves (4 Å) and dried silica gel as the acid catalyst.

Under these conditions, the Schiff bases **3** of aromatic and heteroaromatic aldehydes are obtained in crystalline form (Table I).[5] The amount of the corresponding α-anomer can be restricted to less than 4% even for electron-rich derivatives, e.g. **3a**. Imines **3** of aliphatic aldehydes cannot be isolated in crystalline form by this method. Furthermore, aliphatic imines undergo anomerization at temperatures above −10 °C. The resulting anomer mixtures give rise to complex product mixtures and, consequently, are not useful in the reactions described in this paper. Being dienophiles of relatively low reactivity, the aldimines **3** do not react with dienes, as for instance, isoprene or cyclopentadiene, at room temperature.[6] Also

Scheme I

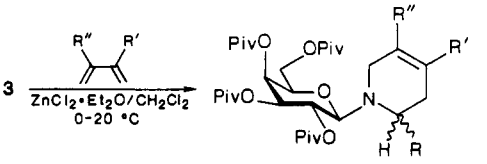


1



3

Scheme II

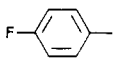
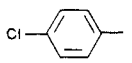


4

(1) Ger. Offen. C 07 H 15/18; Reg. No. P 3624 376.0 (Kunz, H.; Sager, W.; Pfrengle, W.; Decker, M.), July 18, 1986.
(2) Kunz, H.; Sager, W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 557.
(3) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651.
(4) For review, see: Boger, D. L.; Weinreb, S.M. Hetero-Diels–Alder Methodology in Organic Synthesis; Vol. 47 of *Organic Chemistry*; Wasserman, H. H., Ed.; Academic Press: New York, 1987; Vol. 47, Chapter 2, p 34.
(5) The imines **3** have *E* configuration as has been demonstrated by a strong NOE between the imine and the anomeric proton in ^{1}H NMR measurements (see ref 2). It is commonly assumed that acyclic imines exist in *E* configuration. See, for instance: Krow, G. R.; Johnson, C.; Boyle, M. *Tetrahedron Lett.* **1978**, 1971.
(6) In water stereoselective aza-Diels–Alder reactions proceed without catalysis: Larson, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5746. Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 274.

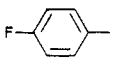
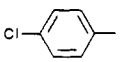
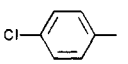
0022-3263/89/1954-4261$01.50/0

Table I. Synthesis of *N*-Alkylidene-2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamines 3 According to Scheme I

imine	R	reaction time, h	yield,[a] %	mp, °C	$[\alpha]^{20}_D$, deg (c = 1, $CHCl_3$)
3a		24	80	72–73	−28.4
3b		24	78	78–79	−14.2
3c[b]		2	87	115	−26.0
3d[b]		1	87	141	−31.2
3e		8	95	amorphous	+7.1

[a] In analytically pure form. [b] Obtained in the presence of catalytic amounts of acetic acid.

Table II. Aza-Diels–Alder Synthesis of *N*-Galactosyldehydropiperidine Derivatives 4 According to Scheme II

imine 3	R	diene R′	diene R″	reaction temp, °C	reaction time, h	product 4	ratio of diastereomers[a]	yield, % α-anomer[e]	yield, % mixture[b]	yield, % pure diastereomer[b,c]
3a		CH_3	H	20	96	**4a**	79:21	–	98	–
3b		CH_3	H	20	96	**4b**	85:15	8	95	–
3c		CH_3	H	4	12	**4c**	90:10	15	90	52
3d		CH_3	H	4	12	**4d**	85:15	12	95	60
3d		CH_3	CH_3	4	12	**4e**	87:13	5	96	71
3e[d]		CH_3	H	20	96	**4f**	69:31	–	98	48

[a] HPLC from hydrolyzed reaction mixture. [b] Correct elemental analysis, structure confirmation by 400-MHz ^1H NMR. [c] After flash chromatography. [d] 2 equiv of $ZnCl_2 \cdot Et_2O$ were used. [e] This product is only detectable by HPLC analysis (diode array detection) and cannot be isolated. Since its UV spectrum is similar to those of the β-diastereomers 4, it is assumed that this compound is a corresponding α-anomer.

in the presence of zinc chloride in tetrahydrofuran, the cycloaddition does not occur. With the more active zinc chloride etherate in dichloromethane, however, aza-Diels–Alder reactions of the imines **3** with either isoprene or 2,3-dimethylbuta-1,3-diene proceed at +4 °C to room temperature to give the *N*-galactosyldehydropiperidine derivatives **4** as a mixture of three diastereomers in high yield (Scheme II and Table II). Under these conditions, cyclopentadiene is subject to polymerization rather than cycloaddition.

The results summarized in Table II show that besides the two β-configurated diastereomers **4**, a third compound is formed, which in neither case could be isolated in pure form and characterized. Due to the similarity of its UV spectrum (HPLC, diode array detection) and those obtained from the β-anomers **4**, we assume that this compound is a corresponding α-anomer.

Since both the imines **3** and the products **4** slowly anomerize under acidic conditions, such an α-anomer can be formed either from the α-anomer imine or from the major β-diastereomer. Inasmuch as the dimethylbutadiene also gives three products showing HPLC retention times exactly corresponding to those found for the isoprene adducts, it is concluded that in the reactions of isoprene no regioisomers are formed.[7] The diastereoselectivity is moderate reaching up to 9:1 (**4c**). However, in four out of six cases pure diastereomers are obtained by flash chromatography. The absolute configuration of the adducts **4** could not be assigned at this stage. In analogy to the Ugi reaction[3] attack at the *si*-site of the C=N bond should be preferred and the major diastereomers should have *S* configuration.

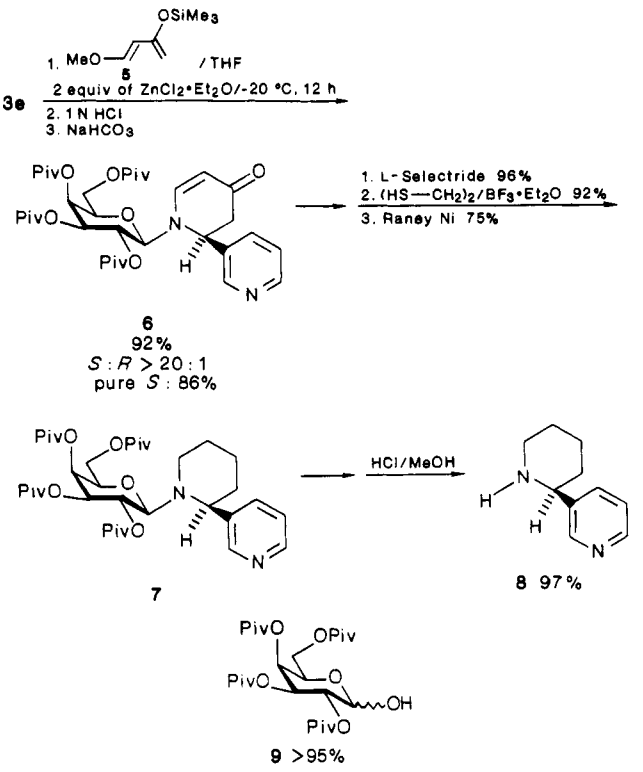
To prove this assumption we proposed to synthesize a natural product of known configuration. In the light of the great potential which the aza-Diels–Alder reaction holds for alkaloid syntheses it appeared to us that the pyridine 3-aldehyde imine **3e** might provide a route to the tobacco alkaloid anabasin. In addition we expected that with more reactive dienes more selective conversions should be achieved at lower temperature. Thus, the 3-pyridyl aldimine **3e** was reacted with 1-methoxy-3-[(trimethylsilyl)oxy]butadiene **5** (Danishefsky's diene[8]).[9] As for the formation of **4f**, the reaction requires 2 equiv of zinc chloride. The first of them obviously is inactivated by coordination to the pyridine nitrogen. The reaction proceeds in tetrahydrofuran at −20 °C. After addition of 1 N HCl, neutralization with sodium bicarbonate solution,

(7) This result is in agreement with the excellent regioselectivity generally observed in imino Diels–Alder reactions, see: Titov, Y. A. *Russ. Chem. Rev.* **1962**, *31*, 267. Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.

(8) For reactions of aldimines with **5** and similar electron-rich dienes, see: (a) Kerwin, J. F., Jr.; Danishefsky, S. *Tetrahedron Lett.* **1982**, *23*, 3739. (b) Danishefsky, S.; Langer, M. E.; Vogel, C. *Tetrahedron Lett.* **1985**, *26*, 5983. (c) Danishefsky, S.; Vogel, C. *J. Org. Chem.* **1986**, *51*, 3915. (d) Vacca, J. P. *Tetrahedron Lett.* **1985**, *26*, 1277.

(9) In the meantime we obtained indications that the reaction of the silyl dienol ether **5** with the imines **3** probably proceeds by a stepwise mechanism.

Scheme III



and extraction with dichloromethane, the *N*-galactosyldehydropiperidinone derivative **6** was isolated in high yield showing a diastereomeric ratio of more than 20:1 (HPLC and 400-MHz ^{1}H NMR). The pure diastereomer **6**[10] was isolated by flash chromatography in about 86% yield (Scheme III).

Compound **6** is then converted into the *N*-galactosylanabasin **7** by reduction of its double bond with L-Selectride,[11] formation of the dithiolane derivative, and its desulfurization with Raney nickel. The final release of the anabasin **8** from the carbohydrate template is achieved almost quantitatively with HCl/methanol. For characterization, **8** is transformed into its *p*-nitrobenzoate.[12] Comparison of the optical rotation with that reported in the literature[13] demonstrated that the (*S*)-anabasin **8** is obtained. Consequently, the (*S*)-diastereomer of **6** is formed in the described cyclocondensation with high diastereoselectivity. During work up the O-pivaloylated galactose **9** can be isolated almost quantitatively and reconverted into the starting auxiliary **1** by a simple sequence of reactions.[2]

In conclusion, the carbohydrate template **1** offers a new and effective method for diastereoselective aza-Diels–Alder synthesis of interesting chiral nitrogen heterocycles. It should be noted that aza-Diels–Alder reactions in asymmetric form have been described only in a few isolated cases.[5,8b,14]

(10) Mp 176 °C; $[\alpha]^{20}_D$ = +19.6° (*c* = 3, $CHCl_3$).

(11) An analogous reaction on uraciles served as the model: Hannon, S. J.; Kundu, N. G.; Herzberg, R. P.; Bhatt, R. S.; Heidelberger, C. *Tetrahedron Lett.* **1980**, *21*, 1105.

(12) **8**, *p*-nitrobenzoate: mp 122 °C; $[\alpha]^{20}_D$ = −130.8° (*c* = 1.2, MeOH) (lit.[10] mp 127–128 °C); $[\alpha]^{20}_D$ = −130.0° (*c* = 3, MeOH).

(13) Späth, E.; Kesztler, F. *Chem. Ber.* **1937**, *70*, 704 and 709.

(14) For diastereoselective hetero-Diels–Alder reactions of chiral nitroso compounds with dienes, see: Felber, H.; Kresze, G.; Braun, H.; Vasella, A. *Tetrahedron Lett.* **1984**, *25*, 5381.

Enzyme-Catalyzed Enantioconvergent Lactonization of γ-Hydroxy Diesters in Organic Solvents

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Summary: A strategy has been developed for the enantioconvergent lactonization of symmetrical hydroxy diesters which exploits the prochiral stereospecificity of lipases in organic solvents. Using this approach, prochiral γ-hydroxypimelate diesters (**2**) were converted into either enantiomer of γ-butyrolactone γ-3-propionates (**3**).

Sir: It is now well established that hydrolytic enzymes can act as catalysts in anhydrous organic solvents,[1] where they catalyze ester synthesis and ester exchange rather than hydrolysis. Following the pioneering work of Klibanov,[2] several lipases (triacylglycerol hydrolases EC 3.1.1.3) have been used for the preparative resolution of chiral acids and alcohols via enantiospecific esterification and transesterification.[3] We recently found that porcine pancreatic lipase suspended in organic solvents catalyzes the stereospecific lactonization of esters of γ- and δ-hydroxy carboxylic acids, and we have used this method to prepare gram quantities of optically pure substituted γ- and δ-lactones.[4,5] A similar approach was developed by Yamada[6] and by Sih[7] for the preparation of macrocyclic lactones under carefully controlled kinetic conditions.

All of these experiments rely on the enantiospecificity of the enzymatic conversions and as such amount to kinetic resolutions of racemic hydroxy esters. The theoretical yield of chiral lactone from such a reaction is 50%, although in practice it will be considerably lower. This is because competitive lactonization of the unwanted enantiomer increases as the reaction progresses, so that the reaction must be stopped at low conversion to optimize optical purity. This problem does not arise if the substrate is prochiral. Enzymes exhibit prochiral stereospecificity, i.e. the ability to discriminate between enantiotopic groups of a prochiral molecule. In principle, the enzymic cyclization of a prochiral hydroxy diester will be enantiocon-

(1) For a review on enzymatic reactions in organic solvents, see: Klibanov, A. M. *Chemtech* **1986**, *16*, 354.

(2) (a) Zaks, A.; Klibanov, A. M. *Science* **1984**, *224*, 1249. (b) Cambou, B.; Klibanov, A. M. *J. Am. Chem. Soc.* **1984**, *106*, 2687. (c) Kirchner, G.; Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 7072.

(3) (a) Langrand, G.; Secci, M.; Buono, G.; Baratti, J.; Triantaphylides, C. *Tetrahedron Lett.* **1985**, *26*, 1857. (b) Stokes, T. M.; Oehlschlager, A. C. *Ibid.* **1987**, *28*, 2091. (c) Belan, A.; Bolte, J.; Fauve, A.; Gourcy, J. G.; Veschambre, H. *J. Org. Chem.* **1987**, *52*, 256. (d) Sonnet, P. E. *Ibid.* **1987**, *52*, 3477. (e) Theisen, P. D.; Heathcock, C. H. *Ibid.* **1988**, *53*, 2374. (f) Chen, C. S.; Wu, S. H.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2812. (g) Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *Ibid.* **1988**, *110*, 7200. (h) Yamamoto, K.; Nishioka, T.; Oda, J.; Yamamoto, Y. *Tetrahedron Lett.* **1988**, *29*, 1717.

(4) Gutman, A. L.; Zuobi, K.; Boltansky, A. *Tetrahedron Lett.* **1987**, *28*, 386.

(5) Gutman, A. L.; Oren, D.; Boltanski, A.; Bravdo, T. *Tetrahedron Lett* **1987**, *28*, 5367.

(6) Makita, A.; Nihira T.; Yamada, Y. *Tetrahedron Lett* **1987**, *28*, 805.

(7) Zhi-Wei, G.; Sih, C. J. *J. Am. Chem. Soc.* **1988**, *110*, 1999.

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