JOC Article

Diastereoselective Synthesis of 2-Aminoalkyl-3-sulfonyl-1,3-oxazolidines on Solid Support

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Received August 2, 2002

Herein we report our investigation on the oxidation of solid-support-bound amino alcohols to their corresponding aldehydes. These aldehydes were converted into diastereomerically pure (>10:1) 2,4-*cis*-2-aminoalkyl-3-sulfonyl-1,3-oxazolidines using optically pure 1,2-amino alcohols. The relative configuration was determined using the nuclear Overhauser effect (NOE). The synthesized oxazolidines, which were obtained in high purities, represent a new, diverse scaffold for the solid-phase synthesis of libraries directed toward a pharmacological target.

Introduction

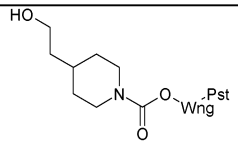
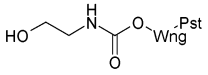
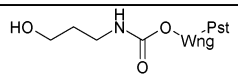
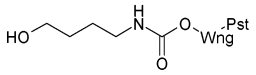
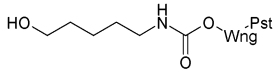
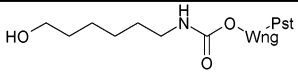
Solid-phase chemistry has become an important tool for combinatorial chemistry, because it allows the easy execution of multistep synthesis in a parallel fashion, preferably done by a robot. Although the number of reactions suitable for solid phase is steadily increasing,[1] there is still a need for new scaffolds, since each scaffold presents its pharmacophoric substituents in one unique spacial arrangement. 3-Sulfonyl-1,3-oxazolidines have been used in the field of stereoselective synthesis, representing a source for a high variety of chiral aldehydes.[2,3] These heterocycles can be built up from three building blocks: a 1,2-amino alcohol with one or two substitutents, a sulfonyl chloride, and an aldehyde. We became interested in this class of compounds as a scaffold for our lead finding program, bearing two hydrophobic groups and one amino alkyl side chain. 3-Sulfonyl-1,3-oxazolidines are stable under acidic conditions (2 N HCl) during reaction workup,[2] so this compound class is expected to be stable for oral administration, which makes it an attractive scaffold for medicinal chemistry.

Herein we report our investigation of the oxidation of amino alcohols to the corresponding aldehydes and their subsequent conversion to highly diastereomerically enriched 2,4-*cis*-2-aminoalkyl-3-sulfonyl-1,3-oxazolidines.

Results and Discussion

The oxidation of resin bound alcohols is well-established. The use of sulfur trioxide-pyridine/triethylamine/dimethyl sulfoxide in dichloromethane seems to be the method of choice for most cases.[4−7] We were interested in resin-bound amino aldehydes, in which the carbamate linker acts as anchor and protecting group for the amine.

TABLE 1. Purities of Obtained Hexahydro-xanthene-diones 6

Amino alcohol (**4**)		Purity[a] of **6**
4a		95%
4b		17%
4c		97%
4d		0%
4e		59%
4f		88%

[a] Determined by LC−MS, ELS trace.

(1) Zaragoza, F. *Organic Synthesis on Solid Phase−Supports, Linkers, Reactions*; Wiley-VCH: Weinheim, 2002.
(2) Bruggemann, M.; Holst, C.; Hoppe, D. *Eur. J. Org. Chem.* **2001**, 647, and references cited therein.
(3) Poli, G.; Maccagni, E.; Manzoni, L.; Pilati, T.; Scolastico, C.; Angiolini, M.; Belvisi, L.; Scolastico, C.; Colombo, L.; Carminati, P.; Pisano, C. *Tetrahedron* **1997**, *53*, 1759, and references cited therein.
(4) Reggelin, M.; Brenig, V.; Welcker, R. *Tetrahedron Lett.* **1998**, *39*, 4801.
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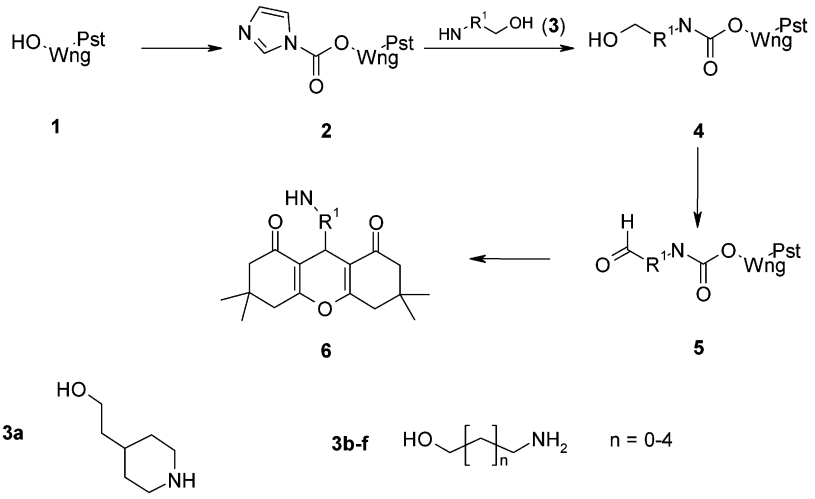
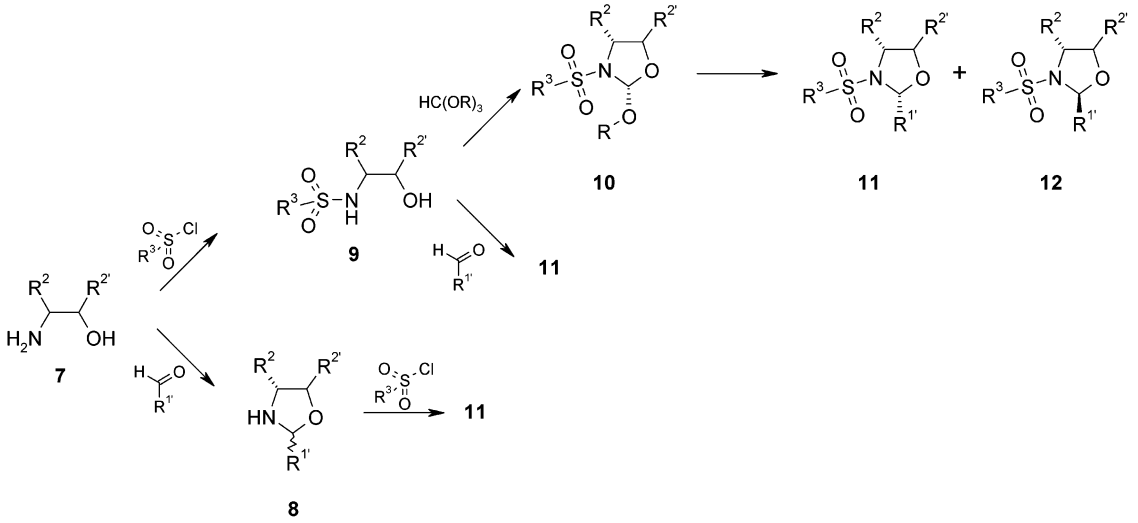
(7) Chen, C.; Randall, L. A. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *Tetrahedron* **1997**, *53*, 6595.

10.1021/jo026278m CCC: $22.00
Published on Web 11/15/2002

SCHEME 1. Oxidation of Solid-Support-Bound Amino Alcohols



SCHEME 2. Routes to 3-Sulfonyl-1,3-oxazolidines



The oxidation of carbamate-protected amino alcohols on solid support has to our knowledge not been investigated yet and can be tricky even in solution under Swern-like conditions[8,9] as a result of the formation of cyclic alkoxycarbamoyl enamines. Therefore we decided to trap the aldehyde with dimedone to yield xanthenes **6**, which are more easily analyzed than the corresponding aldehydes, to determine the efficiency and cleanness of the oxidation step (Scheme 1).

Attachment of the amino alcohols **3** occurred according to described procedures[10] to the Wang linker[11] coupled to polystyrene **1**. The alcohols **4** were then oxidized with sulfur trioxide-pyridine/dimethyl sulfoxide/triethylamine in 1,2-dichloropropane at room temperature overnight. Subsequently we reacted the solid-support-bound aldehydes **5** with dimedone and acetic acid in NMP to yield the hexahydro-xanthene-diones **6** after cleavage (Table 1).

As expected the oxidations of resin bound amino butanol (**4d**) and amino pentanol (**4e**) turned out to be troublesome, most probable as a result of the formation of cyclic alkoxycarbamoyl enamines. Also the oxidation of resin-bound amino ethanol (**4b**) gave only low yields. After establishing the validity of our oxidation procedure for some of the amino alcohols we investigated the possibility of transforming the aldehydes **5** into 3-sulfonyl-1,3-oxazolidines. Using a 1,2-amino alcohol as reagent, there are three main routes to synthesize 2,4,5 substituted 3-sulfonyl-1,3-oxazolidines (Scheme 2).

The two routes based on sulfonamides **9** as intermediates have been well-investigated by the groups of Hoppe[2] and Scolastico.[3] The condensation of sulfonamides **9** with aldehydes gives predominately 2,4-*cis*-oxazolidines **11**,[12] whereas the nucleophilic substitution on 2-alkoxy oxazolidines **10** can yield considerable amounts of 2,4-*trans*-oxazolidines **12**.[13,14] The sulfonation of oxazolidines **8** to give the 2,4-*cis*-3-sulfonyl oxazolidines **11** in homogeneous phase has been described by Takahashi et al.[15]

(8) Yu, C. Z.; Hu, L. Q. *Tetrahedron Lett.* **2001**, *42*, 5167.
(9) Lee, B. H.; Miller, M. J.; Prody, C. A.; Neilands, J. B. *J. Med. Chem* **1985**, *28*, 317.
(10) Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589−1592.
(11) Wang, S. S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.
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(13) Conde-Frieboes, K.; Hoppe, D. *Synlett* **1990**, 99.
(14) Conde-Frieboes, K.; Hoppe, D. *Tetrahedron* **1992**, *48*, 6011.

SCHEME 3. Synthesis of 3-Sulfonyl-1,3-oxazolidines 16

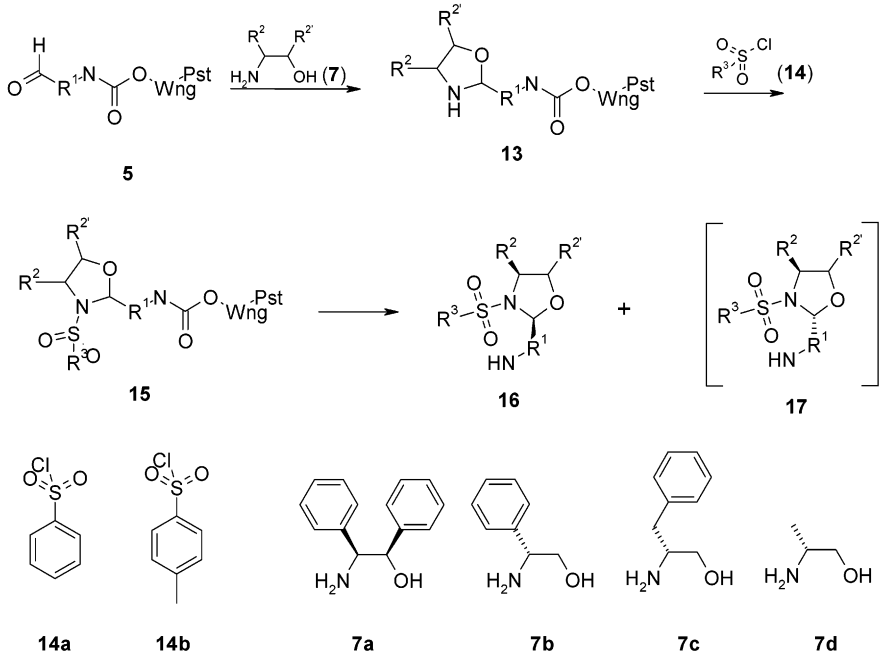

TABLE 2. Purities (%)[a] of Oxazolidines 16 (all >10:1 *cis:trans*)[b]

	3a		3c		3f	
	14a	**14b**	**14a**	**14b**	**14a**	**14b**
7a	87	97	98	100	60	78
7b	84	96	95	98	80	46
7c	64	80	100	100	47	66
7d	81	92	100	97	88	95

[a] Determined by LC−MS, ELS trace. [b] Determined by ^{1}H NMR.

We followed the last example because it provides more flexibility due to the fact that all building blocks can be used directly, without prior derivatization or protection. Following the upper route would require the synthesis of the sulfonamides **9** prior to library synthesis, sacrificing one of the advantages of the solid-phase approach.

We treated the solid-support-bound aldehyde **5** with the amino alcohol **7** and 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one as acidic catalyst in *N*-methyl pyrrolidone, followed by sulfonation with arene sulfonyl chlorides and triethylamine in *N*-methyl pyrrolidone (Scheme 3) to yield the 2,4-*cis*-2-aminoalkyl-3-sulfonyl-1,3-oxazolidines **16** after cleavage from the solid support with 1:1 dichloromethane/trifluoroacetic acid.

All samples were analyzed by LC−MS and ^{1}H NMR. The results are summarized in Table 2.

Analysis by LS−MS revealed only one isomer **16**, and we assumed it to be the 2,4-*cis*-isomer.[15] In the 1D ^{1}H NMR spectra a set of signals attributable to the second isomer **17** was detectable but never reached more than 8% (11.5:1) of the major isomer. In some cases the second isomer was not detectable by NMR. The major impurities were eluting with the solvent peak in the LC-MS, being most probable residual salts from insufficient washing. The structures were confirmed by sets of NMR experiments (HSQC,[16] HMBC,[17] and selective TOCSY[18]). Furthermore, to establish the relative configuration we performed selective NOE[19] experiments for representative cases (Figure 1),[20] and in the instance of **16cab** we

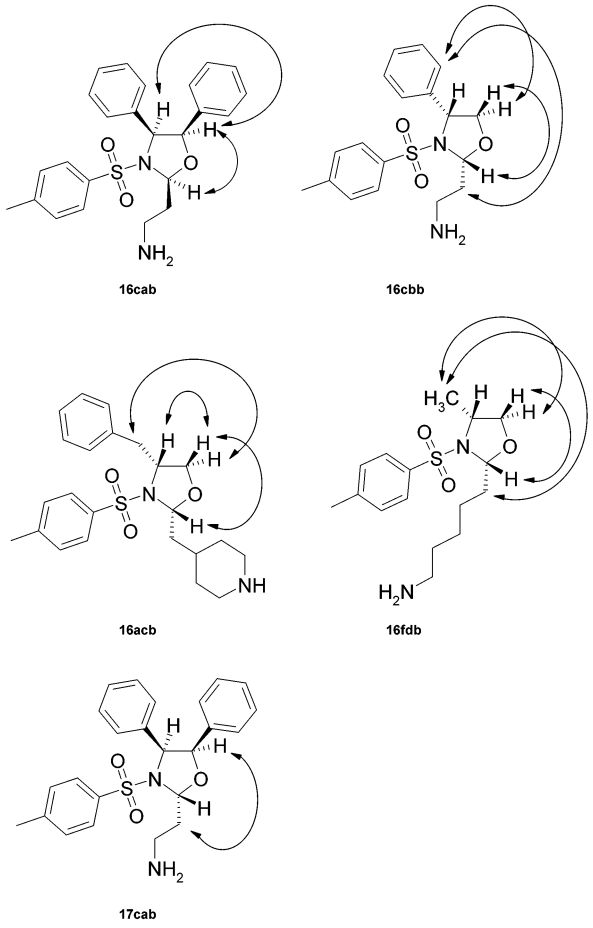

FIGURE 1. Diagnostic NOEs on four oxazolidines **16** and **17cab**.

(15) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Heterocycles* **1992**, *33*, 281.

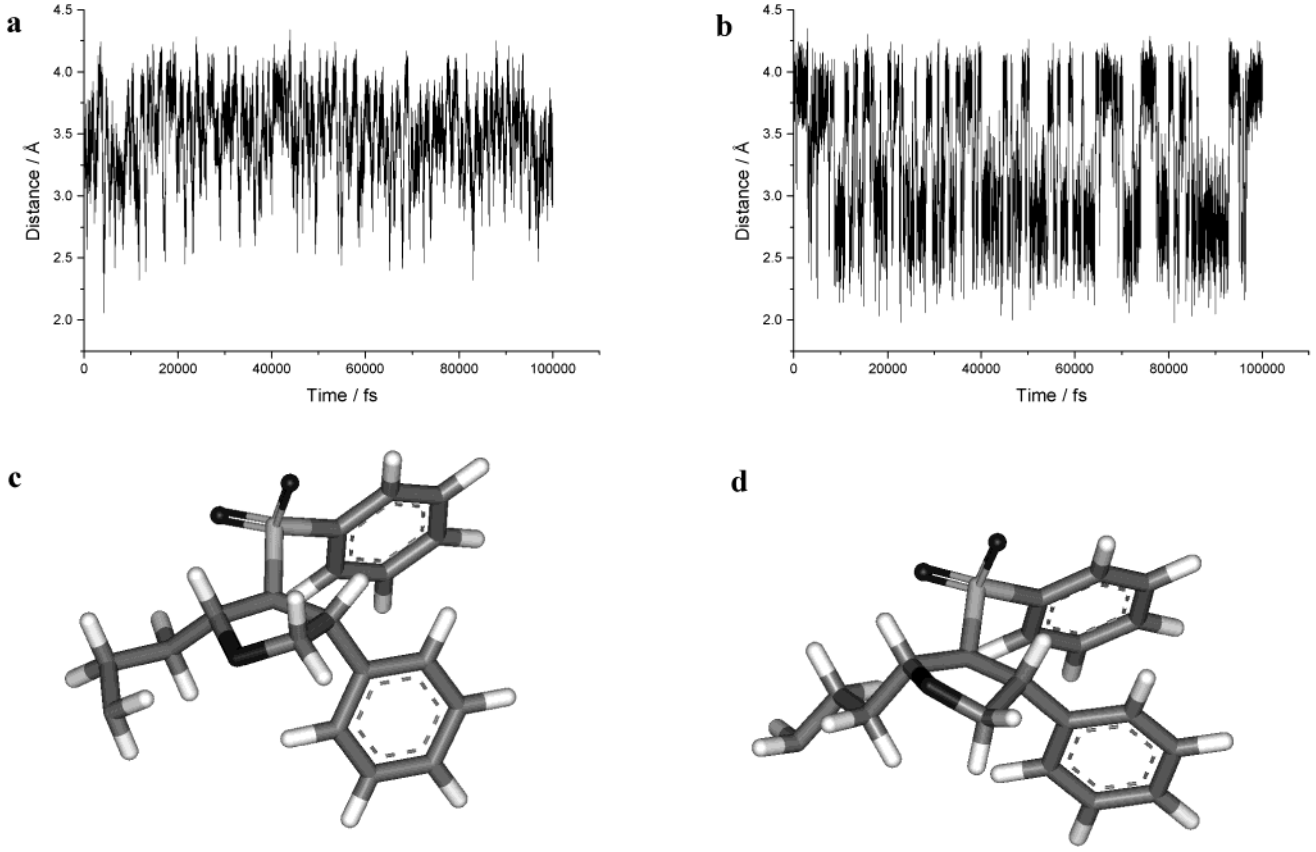

FIGURE 2. Results of MD calculations on **16cba** over 100 ps. (a) Trajectory of the distance 2-H and 4-H. (b) Trajectory of the distance 2-H and 5-H *cis*. (c) Energy minimized structure **16cba-O(1)-*endo*** at time point 23775 fs, $d_{(2-4)}$ 3.53 Å, $d_{(2-5cis)}$ 2.69 Å. (d) Energy minimized structure **16cba-C(5)-*endo*** at time point 75190 fs, $d_{(2-4)}$ 3.44 Å, $d_{(2-5cis)}$ 3.95.

were able to identify the diagnostic signals for the minor isomer **17cab**.

Except for the 2,4-*trans*-oxazolidine **17cab** strong correlations were observed between the proton in the 2-position and one of the protons in the 5-position for examples **16cab**, **16cbb**, **16acb**, and **16fdb**. A correlation between the proton in the 2-position and the proton in the 4-position was generally missing or very weak, except for **16cab**, which may adapt a slightly different conformation than the other examples due to the additional substituent in the 5-position. The interactions between the substituents in the 2- and 4-positions across the ring turned out to be of most value for concluding the relative stereochemistry. In the case of **16cbb** and **16fdb** a correlation was observed between the methylene group attached to the 2-position and the substituent in the 4-position, which also correlates to the *pro-S* proton in the 5-position. The correlation between the substituent in 4-position and the *pro-S* proton in the 5-position combined with the correlation of the proton in 2-position to the *pro-R* proton in the 5 position supports also the 2-4-*cis* configuration assigned to **16acb**.

To clarify the reasons for the weak or missing interactions between the protons in the 2-position and 4-position we conducted molecular dynamics calculations on example **16cba**. In the trajectory for the distance between the protons in the 2-position and in the *cis*-5-position we discovered two conformers, which were interchanging rapidly (Figure 2). We randomly picked one representative of each set of conformers and energy minimized the structures. In both conformers the distance between the protons in the 2-position and the 4-position was around 3.5 Å, whereas the distance between the protons in the 2-position and the 5-*cis*-position ranged between between 2.69 Å (**16cba-O(1)-endo**) and 3.95 Å (**16cba-C(5)-endo**). With the relativly short mixing time (400 ms) used in the NOE experiments, only short range interactions were observable, implying that only the interaction between protons at positions 2 and 5-*cis* in conformer **16cba-O(1)-endo** was resulting in a detectable NOE signal.

The oxazolidines **16** were obtained in high diastereomeric purity. To confirm that we had a highly diastereoselective reaction on solid support and not an epimerization under cleavage conditions, in view of the fact that 2,4-*trans*-3-sulfonyl-oxazoldines can epimerize on the stereogenic center at C-2 to yield 2,4-*cis* isomers under Lewis acidic conditions,[13] we conducted some high-

(16) Schleucher, J.; Schwendinger, M.; Sattler, M.; Schmidt, P.; Schedletzky, O.; Glaser, S. J.; Sorensen, O. W.; Griesinger, C. *J. Biomol. NMR* **1994**, *4*, 301.
(17) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
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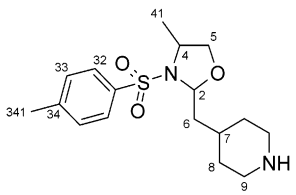
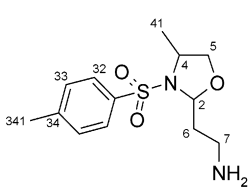
(19) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302.
(20) For numbering of the final products we apply the indices of the building blocks used, e.g., the oxazolidine build from **3c**, **7a**, and **14b** gets the number **16cab**.

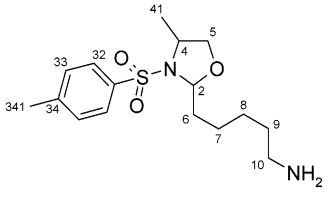
TABLE 3. Selected NMR Data of Oxazolidines 16 (Proton Shift, Carbon Shift, Proton Coupling Constants)[a]

	2	4	5	6	7	8	9	10	41	32	33	34/341
16aaa	5.09	5.20	4.62	2.28/2.07	1.97	1.95/1.40	3.30/2.90			7.99	7.69	7.78
	89.9	65.5	82.8	41.8	30.4	28.4	43.4			128.0	130.0	134.1
	9.1/1.5	6.3	6.3									
16aab	5.04	5.29	4.60	2.27/2.06	1.96	1.97/1.45	3.29/2.89			7.89	7.51	2.44
	89.9	65.4	82.8	41.8	30.4	28.8	43.4			128.1	130.4	21.2
	9.1/1.5	6.3	6.3									
16caa	5.17	5.20	4.59	2.65/2.40	3.15					8.04	7.71	7.80
	88.9	65.5	82.6	33.5	35.6					128.1	129.9	134.1
	8.6/2.5	6.3	6.3									
16cab	5.13	5.18	4.59	2.64/2.39	3.26					7.93	7.52	2.44
	89.0	65.6	82.6	33.7	35.7					128.3	130.4	21.2
	2.5/8.7	6.3	6.3									
16faa	5.00	5.21	4.62	2.30/2.05	1.58	1.33	1.55	2.80		7.99	7.69	7.78
	91.5	65.6	82.5	35.2	24.3	25.6	27.0	38.9		128.0	129.9	133.9
	2.0/8.6	6.3	6.3									
16fab	4.96	5.19	4.61	2.29/2.05	1.58	1.32	1.57	2.81		7.88	7.50	2.43
	91.5	65.6	82.4	35.3	24.3	24.4	27.0	38.9		128.0	130.3	21.2
	2.0/8.6	6.3	6.3									
16aba	5.20	4.79	3.78/3.85	1.77	1.87	1.83/1.33	3.25/2.86			7.94	7.69	7.78
	90.8	61.8	72.1	41.4	30.0	28.4	43.3			128.1	129.9	134.0
	7.8/3.3	5.3/7.0	5.3/9.1/7.0/9.1									
16abb	5.18	4.77	3.84/3.79	1.76	1.79	1.84/1.34	3.26/2.85			7.81	7.49	2.43
	90.7	61.6	72.1	41.5	30.0	28.4	43.2			128.2	130.3	21.1
	7.8/ 3.3	5.1/6.8	5.1/9.1/6.8/9.1									
16cba	5.32	4.79	3.86/3.79	2.20/2.09	3.00/2.91					7.98	7.70	7.80
	90.0	61.8	72.2	33.2	35.4					128.3	129.9	134.1
	7.8/4.0	5.3/7.1	5.3/9.3/7.1/9.3									
16cbb	5.30	4.76	3.85/3.80	2.18/2.08	3.00/2.90					7.86	7.50	2.43
	90.0	61.8	72.1	33.2	33.2					128.3	130.3	21.1
	7.8/4.2	5.2/6.8	5.2/9.2/6.8/9.2									
16fba	5.11	4.80	3.83/3.77	1.87/1.73	1.40	1.33	1.54	2.78		7.92	7.67	7.77
	92.4	61.6	72.0	35.0	24.1	25.5	27.0	38.9		128.1	129.8	134.0
	4.0/7.6	5.1/6.6	5.1/9.1/6.6/9.1									
16fbb	5.09	4.77	3.78	1.84/1.72	1.39	1.32	1.52	2.78		7.82	7.49	2.43
	92.4	61.6	71.9	35.1	24.1	25.6	27.1	38.9		128.1	130.3	21.1
	4.0/7.6	5.6/7.1	5.6/9.1 /7.1/9.1									
16aca	5.04	3.82	3.67/3.32	1.49	1.70	1.82/1.30	3.27/2.85		3.01/2.90	7.92	7.66	7.75
	90.2	59.7	68.5	41.4	29.7	28.4	43.3		40.0	128.0	129.8	133.9
	4.4/7.6	m	5.1/9.1/6.6/9.1									
16acb	5.02	3.81	3.66/3.32	1.48	1.69	1.81/1.30	3.25/2.86		3.01/2.89	7.79	7.45	2.40
	90.2	59.7	68.5	41.6	29.6	28.4	43.3		40.0	128.0	130.3	21.1
	4.4/7.6	m	5.1/9.1/6.6/9.1									
16ccca	5.15	3.85	3.68/3.24	2.00	2.92				3.04/2.83	7.95	7.67	7.76
	89.4	60.0	68.8	33.3	35.2				40.4	128.1	129.9	134.0
	4.6/7.1	m	4.3/9.1/6.3/9.1									
16cccb	5.13	3.82	3.67/3.25	2.00	2.93				3.04/2.83	7.83	7.46	2.41
	89.5	60.0	68.8	33.3	35.2				40.4	128.1	130.3	21.1
	4.6/7.0	m	4.4/9.1/6.3/9.1									
16fca	4.94	3.84	3.64/3.26	1.58	1.34	1.31	1.54	2.79		7.91	7.65	7.73
	91.9	59.9	68.4	35.2	23.9	25.6	27.1	38.9		128.0	129.9	133.8
	4.3/7.1	m	4.7/9.1/6.4/9.1									
16fcb	4.91	3.80	3.61/3.26	1.56	1.33	1.31	1.53	2.78		7.77	7.43	2.39
	92.0	60.0	68.6	35.3	23.7	25.7	27.2	39.1		128.2	130.4	21.2
	4.3/7.1	m	4.8/9.1 /6.6/9.1									
16ada	5.03	3.70	3.53/3.44	1.68	1.76	1.85/1.34	3.25/2.86		1.25	7.87	7.65	7.75
	90.2	54.7	70.9	42.0	29.9	28.5	43.3		20.7	127.9	129.8	133.8
	5.1/7.1	m	5.0/9.0/6.6/9.0									
16adb	5.07	3.68	3.52/3.45	1.66	1.76	1.85/1.33	3.25/2.85		1.24	7.76	7.45	2.41
	90.2	54.7	70.9	42.0	29.9	28.5	43.2		20.7	127.9	130.2	21.1
	4.8/7.0	m	5.0/9.0/6.8/9.0									
16cda	5.13	3.72	3.54/3.43	2.07	2.93				1.25	7.91	7.66	7.76
	89.3	54.9	71.2	33.5	35.2				20.7	128.0	129.8	133.9
	4.7/6.8	m	4.8/8.8/6.3/8.8									
16cdb	5.11	3.69	3.53/3.44	2.04	2.93				1.24	7.79	7.46	2.14
	89.3	54.8	71.1	33.4	33.2				20.6	128.1	130.2	21.1
	4.6/7.1	m	5.0/9.1/6.6/9.1									
16fda	4.93	3.73	3.51/3.39	1.72	1.38	1.34	1.55	2.79	1.24	7.87	7.65	7.74
	90.7	54.7	70.9	35.5	23.6	25.5	27.0	38.9	20.7	127.9	129.7	133.7
	4.0/7.3	m	4.8/9.1/6.6/8.8									
16fdb	4.91	3.68	3.49/3.40	1.71	1.38	1.34	1.55	2.78	1.23	7.75	7.45	2.41
	91.7	54.8	70.9	35.4	23.7	25.6	27.0	38.9	20.7	127.9	130.1	21.2
	4.0/7.1	m	4.4/8.8/6.6/8.8									

[a] Chemical shift are given relative to internal TMS in d_6-DMSO, carbon shifts are taken from 2D-HSQS spectra.







resolution magic angle spinning NMR (HR-MAS NMR)[21,22] experiments on **15faa** prior to the cleaving step. In a 2D $^{1}H,^{13}C-HSQC$ experiment we found only one set of the characteristic signals for the oxazolidine ring (2-C 91.9, 2-H 5.22, 4-C 66.6, 4-H 5.03, 5-C 83.5, 5-H 4.80 (all ppm)) bound to the resin, sustaining our claim of a highly diastereoselective synthesis on solid support. The chemical shifts recorded on solid support are similar to the values observed for the final product **16faa**. To summarize our observations: (1) We observed only one resin-bound diastereomer (**15faa**). (2) Upon cleavage we obtained only one diastereomer, namely, the 2,4-*cis* isomers **16**. (3) Comparison of the chemical shifts of **15faa** and **16faa** indicates **15faa** to have the same stereochemistry as **16faa**. We do not know whether the oxazolidines could epimerize under clevage conditions because at no time point did we have sufficient amounts of the thermodynamically unfavored 2,4-*trans* oxazolidine **17** to test this.

Herein we have described a new five-step sequence (including attachment of the amino alcohol and cleavage of the final product) proceeding cleanly and enabling the quick preparation of enantiomerically and diastereomerically pure and diverse 2,4-*cis*-2-aminoalkyl-3-sulfonyl-1,3-oxazoldines, a new scaffold bearing three R-groups. We have proven their relative configuration by selective nuclear Overhauser experiments, supported by Molecular Dynamics calculations, and brought NMR evidence forward to confirm our claim for a diastereoselective synthesis on solid support.

Experimental Section

General Methods. Liquid chromatographic analysis was conducted on a C18 column with MS, UV, and ELS detectors using a 0.01% TFA/acetonitril gradient. The amino alcohols **7** were purchased as the enantiomers shown in Scheme 3. All reagents and solvents were obtained commercially and were used without further purification.

NMR spectra were recorded on a 400- or 600-MHz instrument equipped with 5 mm selective inverse ($^{1}H,^{13}C$) *z*-gradient probe heads. For all compounds 1D ^{1}H and 2D $^{1}H,^{13}C$-HSQC spectra were recorded, which for selected compounds were supplemented by 2D COSY, 1D and 2D TOCSY, and 2D HMBC experiments. Relative configurations were determined by selective 1D NOE measurements.[19] Selective excitation in the 1D TOCSY and NOE experiments was achieved by the double pulsed field gradient spin-echo sequence[18,19] by Gaussian-shaped 180° pulses (truncated at the 1% level) ranging from 35 to 90 ms in length depending on the desired selectivity. MD calculation were performed using the MMFF94[23−27] force field as implemented in Sybyl 6.7. The dielectric constant was set to 4.0. The simulations were carried out at 500 K for 100 ps. Temperature coupling was set to 10 fs. The carbonyl imidazol loaded Wang linker **2** was prepared according to the procedure by Hauske.[10]

Synthesis of Amino Alcohol Loaded Resin 4. Amino alcohol **3** (10 equiv) in 2 mL of *N*-methyl pyrrolidone (NMP) was added to 100 mg of resin **2** (∼1.0 mmol/g) in a suitable reactor on a small shaker, and the mixture was agitated for 4 h at 40 °C. The reactors were then cooled to 25 °C, and the resin was washed five times with 3 mL of dichloromethane (DCM).

Synthesis of Amino Aldehyde Loaded Resin 5. Triethylamine (TEA) (0.5 mL) and 10 equiv of sulfur trioxide-pyridine complex in 1 mL of dimethyl sulfoxide (DMSO) were added to 100 mg of resin **4** in 1 mL of 1,2-dichloropropane (DCP), and the mixture was shaken for 16 h at 25 °C. The resin was then washed five times with 3 mL of DCM.

Conversion of Aldehydes to Corresponding 3,3,6,6-Tetramethyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-diones 6. Dimedone (10 equiv) in 2 mL of NMP and 100 μL of acetic acid were added to 100 mg of resin **5**, and the mixture was shaken for 5 h at 25 °C. The resin was washed five times with 3 mL of DCM, and the product was cleaved with 1 mL of DCM and 1 mL of trifluoroacetic acid (TFA) for 50 min at 25 °C. The solvent was removed in a nitrogen stream, and the samples were taken up in 1 mL of methanol for LC-MS analysis.

Synthesis of 3-Sulfonyl-1,3-oxazolidines 16. 1,2-Amino alcohol **7** (4 equiv) and 2 equiv of 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (HODhbt) in 2 mL of NMP were added to 100 mg of resin **5**, and the mixture was agitated for 4 h at 25 °C. The liquid phase was removed by suction, and 0.5 mL of TEA and 10 equiv of sulfonic acid **14** in 1 mL of NMP were added. The reactor was shaken for 19 h at 25 °C. The resin was then washed three times with 3 mL of NMP and 10 times with 3 mL of DCM. The oxazolidines were cleaved from the resin with 2 mL of 1:1 DCM/TFA for 30 min at 25 °C. The solvent was removed in a nitrogen stream, and the samples were taken up in 1 mL of methanol for LC-MS analysis. Selected NMR data are listed in Table 3.

Acknowledgment. We thank Dr. Inge Thøger Christensen and Dr. Florencio Zaragoza Dörwald for helpful discussions.

JO026278M

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