Nuclear analogs of β-lactam antibiotics. XVI. Aldol condensations of N-protected 4-tritylthio-2-azetidinones

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Received September 1, 1982

ALAIN MARTEL, JEAN COLLERETTE, JACQUES BANVILLE, JEAN-PAUL DARIS, PHILIPPE LAPOINTE, BERNARD BELLEAU, and MARCEL MÉNARD. Can. J. Chem. **61**, 613 (1983).

The reaction of acetaldehyde with enolates of N-protected 4-tritylthio-2-azetidinones **4***b* and **4***c* was studied. While the lithium enolate of *N*-methoxymethylazetidinone **4***b* gave only *trans S** 3-(1′-hydroxyethyl)azetidinone **8** the corresponding tetrabutylammonium enolate gave a mixture of *trans R** and *trans S** azetidinones **8** and **9**. The metal enolate of *N*-(*tert*-butyldimethylsilyl)-4-tritylthio-2-azetidinone **4***c* gave all four possible isomers.

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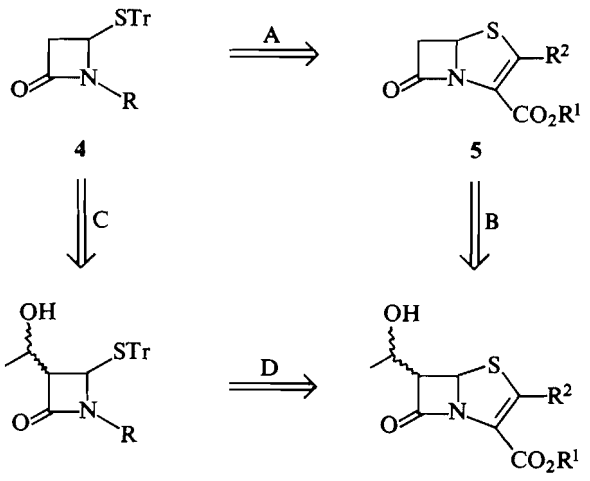
On a étudié la réaction de l'acétaldéhyde avec les énolates des tritylthio-4 azétidinones protégées au niveau de l'azote (**4***b* et **4***c*). Alors que l'énolate lithié de la *N*-méthoxyméthylazétidinone (**4***b*) donne uniquement la *S** (hydroxy-1 éthyl)-3 azétidinone *trans* (**8**) l'énolate correspondant du tétrabutylammonium donne un mélange des azétidinones *R** *trans* et *S** *trans* (**8** et **9**). L'énolate métallique de la *N*-(*tert*-butyldiméthylsilyl) tritylthio-4 azétidinone-2 (**4***c*) donne les 4 isomères possibles.
[Traduit par le journal]

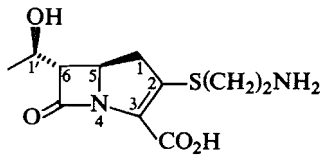
Thienamycin (**1**) (1) and the structurally related olivanic acids (**2**) (2) are characterized, unlike classical β-lactam antibiotics, by a 6-(1′-hydroxyethyl) side chain. Although their configurations at positions 1′ and 6 are inverted, both display remarkable antibacterial properties. Their discovery has generated intensive synthetic work directed towards stereospecific incorporation of such 6-side chains not only to the carbapenem nucleus but also to the related penems (**3**) (3–5). In paper XV (6*a*) of this series we described our own effort at converting preformed 6-unsubstituted penems (**5**) to 6-(1′-hydroxyethyl)



a R = H; *b* R = CH_2OCH_3; *c* R = $Si(CH_3)_2tC_4H_9$

SCHEME 1

and other 6-substituted penems (**7**, **3**): metallation of **5** followed by aldol condensation to acetaldehyde (Scheme 1B) was found to afford a single "unnatural" diastereomeric (1′*R**, 5*R**, 6*R**) 6-hydroxyethylpenem ruling out the use of preformed penems for the preparation of "natural" isomers of **7**.



(1′*R*, 5*R*, 6*S*)

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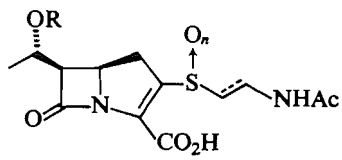
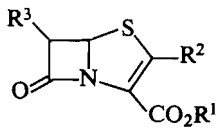


(1′*S*, 5*R*, 6*R*)

2 *n* = 0,1
R = H, SO_3H



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To overcome this problem and at the same time retain the versatile methodology developed for the preparation of 6-unsubstituted penems (Scheme 1A) (6*b*) we required an easy conversion of the key intermediate **4** to properly 6-substituted intermediates like **6** which would allow extension of Scheme 1A to Scheme 1D. This paper describes transformation of **4**, via aldol condensation, to all four possible isomers of **6**. Subsequent papers will report stereospecific conversions of **4** to "natural" **6** where the nitrogen protecting group actually consists of the Woodward phosphoranylidene acetic ester residue required to complete the annulation of the thiazole ring.

N—C-3 Dimetallation of azetidinone **4***a* and aldol reaction with acetaldehyde, in a manner similar to that described by Durst *et al.* (7) for 4-alkylazetidinones, would have provided the shortest method for the introduction of the 3-hydroxyethyl substituent. Possibly because of the different nature of the 4-substituent, azetidinone **4***a* proved to be completely unstable, even at −78°C, to dimetallation conditions. On the other hand, properly N-1 protected **4** were found to give stable monometallated enolates that underwent aldol condensation to

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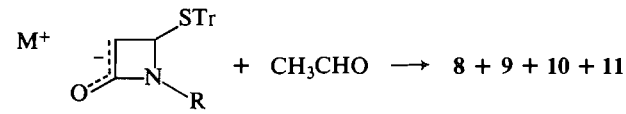
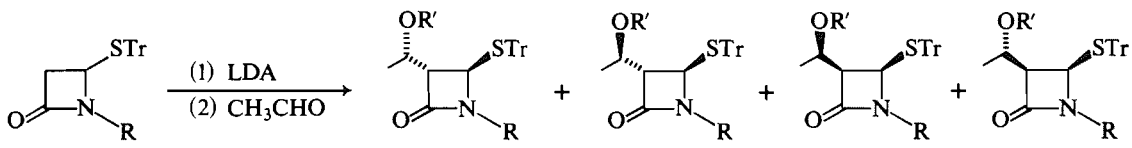
TABLE 1. Stereochemical composition of the aldol condensations



Expt. no.	Starting material	R	M^+	Solvent[a]	Yield, %	8	9	% *trans*	10	11	% *cis*
1	**4***b*	CH_2OCH_3	Li	THF	80	100	0	100	0	0	0
2	**4***b*	CH_2OCH_3	Bu_4N	THF	33[d]	52	48	100	0	0	0
3	**4***c*	Si(CH3)2tBu	Li	THF	92	39	32	71	12	17	29
4	**4***c*	Si(CH3)2tBu	Li	Ether[b]	90	38.2	30.5	68.7	18.4	12.9	31.3
5	**4***c*	Si(CH3)2tBu	Li	Ether[c]	90	44	24.6	68.6	18	13.4	31.4
6	**4***c*	Si(CH3)2tBu	MgBr	Ether	95	30.1	19.7	49.8	31	19.2	50.2
—	**17**[e]	Si(CH3)2tBu	Li	THF	92	37	46	83	14	2	16

[a]Reaction to −78°C except for Expt. 5; reaction time 10 min except for Expts. 4 and 5.
[b]Reaction quenched (HCl) after 1 min.
[c]Reaction mixture allowed to warm to 20°C and stirred 2 h.
[d]62% **4***b* recovered unchanged.
[e]Reference 14.



a R = R′ = H; *b* R = CH_2OCH_3, R′ = H; *c* R = $Si(CH_3)_2tC_4H_9$, R′ = H;

d R = $Si(CH_3)_2tC_4H_9$, R′ = CO_2PNB

SCHEME 2

acetaldehyde in high yields. Two types of protecting group were selected: a sterically small group, with potential metal chelating properties, the methoxymethyl group, and a sterically demanding, chemically inert, N-substituent, the *tert*-butyldimethylsilyl group.

Methoxymethylation of **4***a* was carried out by quenching the nitrogen anion (NaH, THF, MeOH) with bromomethyl methyl ether and afforded crystalline **4***b* in 91% yield. Silylation of **4***a* with *tert*-butyldimethylsilyl chloride in DMF in the presence of triethylamine provided crystalline **4***c* in 89% yield.

The protected azetidinones, **4***b* and **4***c*, were conveniently metallated in an appropriate solvent (Table 1) at −78°C by addition of a slight excess (1.1 equiv.) of preformed LDA (8). Aldol condensation to acetaldehyde was effected under what are assumed to be conditions of kinetic control (−78°C, 10 min) (9*a*). Metal interchange, when required, was achieved by adding an equivalent of anhydrous magnesium bromide (10), zinc chloride (10), or tetrabutylammonium fluoride (11) to the lithium enolate prior to addition of acetaldehyde. Reaction products were separated and purified by hplc. The stereochemical composition of the aldol products under a variety of conditions is summarized in Table 1.

Stereochemical assignments were determined from ^{1}Hmr coupling constants correlation as listed in Table 2.[4] The *cis*−*trans* relationships were readily established on the basis that for 2-azetidinones $J_{3-4}cis > J_{3-4}trans$ (12). It followed that isomers **10***c* and **11***c* with J_{3-4} = 4.5 and 4.6 Hz possessed a *cis* arrangement and **8***b*, **9***b*, **8***c*, and **9***c*, with J_{3-4} = 0.9−2.5 Hz, a *trans* geometry. Configurations at position 1′ were assigned from the observation first made by House *et al.* (10), and corroborated by others in the β-lactam area (4, 5, 13, 14) that, for aldol condensation products, J_{ab} is larger

[4]All compounds described in this paper are racemic mixtures. Structural formulae and stereochemical designations refer to the enantiomer related to natural products, thienamycin and olivanic acid.

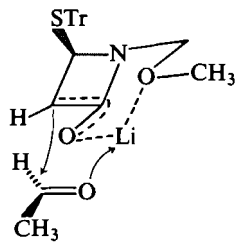
TABLE 2. ^{1}H nuclear magnetic resonance spectra[a]

Compound	H-1′	$J_{1'-3}$	H-3	J_{3-4}	H-4	CH_3	$J_{1'-2'}$	Arom.	Others
8*b*	2.83	4.6	3.06 (dd)	2.0	4.42 (d)	1.12 (d)	6.3	7.1–7.5	4.37 (ABq, 2H), 3.17 (s, 3H), 1.35 (bs, 1H)
8*c*	2.85 (dq)	2.7	3.02 (dd)	1.8	4.32 (d)	1.02 (d)	6.0	7.1–7.6	0.95 (s, 9H), 0.25 (s, 6H)
8*d*	3.72 (dq)	1.8	3.10 (bt)	1.8	4.08 (d)	1.20 (d)	6.5	7.1–7.6 8.2 (d)	5.1 (s, 2H), 1.0 (s, 9H) 0.28 (s, 3H), 0.31 (s, 3H)
9*b*	3.65	5.5	3.3 (dd)	2.5	4.28 (d)	1.05 (d)	6.5	6.9–7.5	4.2 (2H), 3.15 (s, 3H), 1.55 (bs, 1H)
9*c*	3.15–3.55 (m)	3.7	3.32	0.9	4.02			7.2–7.6	0.87 (m, 12H), 0.12 (s, 3H), 0.10 (s, 3H)
9*d*	4.5 (b sextet)	6.0	3.58 (dd)	1.5	3.97 (d)	1.1	6.0	7.1–7.5 8.17 (d)	5.1 (s, 2H), 0.7 (s, 9H), 0.2 (s, 6H)
10*c*	2.39 (dq)	0.9	3.02 (dd)	4.5	4.70 (d)	1.0 (d)	6.5	7.2–7.5	0.97 (s, 9H), 0.36 (s, 3H), 0.34 (s, 3H)
10*d*	3.52 (dq)	0.5	2.95 (dd)	4.5	4.74 (d)	1.1	6.5	7.1–7.6 8.16 (d)	5.30 (ABq, 2H), 1.07 (s, 9H), 0.37 (s, 6H)
11*c*	3.78 (dq)	8.2	3.10 (dd)	4.6	4.30 (d)	1.22 (d)	6.3	6.8–8.0	0.95 (s, 9H), 0.22 (s, 3H), 0.17 (s, 3H)
11*d*	4.53 (b sextet)	5.8	3.32 (dd)	4.8	4.31 (d)	1.44 (d)	6.0	7.1–7.5 8.15 (d)	4.95 (ABq, 2H), 0.95 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H)

[a]Recorded at 80 MHz in $CDCl_3$ using tetramethylsilane as internal standard. Chemical shifts are in δ (ppm) and coupling constants in Hz.

for the *threo* (*trans R**, *cis S**) than for the *erythro* (*trans S**, *cis R**) isomer. Accordingly the *trans* compounds **9***b*, **9***c*, and **9***d*[5] with $J_{1'-3}$ = 5.5, 3.7, and 6.0 Hz were assigned a *R** configuration and the corresponding **8***b*, **8***c*, and **8***d*, with smaller $H_{1'}-H_3$ coupling constants (4.6, 2.7, and 2.0 Hz), a *S** arrangement. The *cis* isomers **11***c* and **11***d* with $J_{1'-3}$ = 8.2 and 5.6 Hz were given the *S**, and **10***c* and **10***d*, with 0.9 and 0.5 Hz, the *R** configuration.

It has been shown by Dubois *et al.* (15), Heathcock and co-workers (9), House *et al.* (10), and Evans *et al.* (16) that aldol stereoselection is governed by a pericyclic process involving the incoming aldehyde, the enolate anion, and the metal countercation. In this hypothesis the stereochemical control of the reaction is effected by the various steric nonbonded interactions in the pseudocyclic transition state. The capacity of the metal cation to accommodate ligands and the polarity of the solvent were also shown to exert an influence on the formation of the cyclic intermediate. Scheme 3 depicts such intermediates for the products of Table 1.



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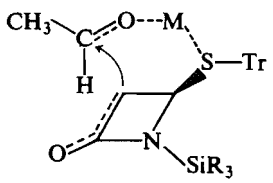

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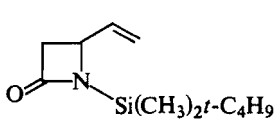

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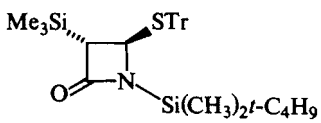

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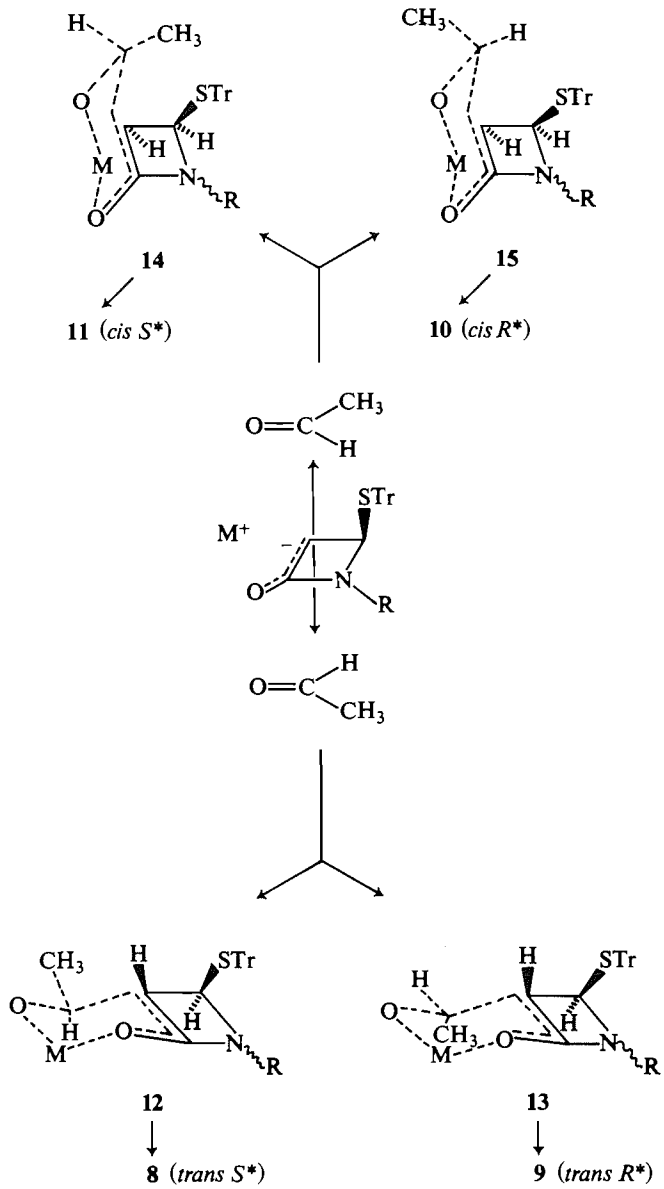
[5]Reaction conditions will appear in a future publication.

In the absence of sterically demanding substitution on the nitrogen atom of the azetidinone (Expts. 1 and 2, Table 1) the bulky tritylthio group at 4β directed hydroxylation exclusively to the less hindered α-face of the molecule; no *cis*-aldols were detected in the reaction mixture. The surprisingly high stereochemical control observed with the lithium enolate of **4***b* (Expt. 1), giving exclusively the *S** configuration at position 1′, likely resulted from a combination of two concurrent effects: because of the pseudo 1,3-diaxial interaction with the C-4α-proton in transition state **13**, the methyl group of the incoming aldehyde should end up principally in the equatorial position (**12**) giving the *trans S** **8***b* as the major isomer; internal lithium chelation in the enolate, **16**, prior to addition of acetaldehyde, according to an hypothesis advanced by Meyers and Reider (17) to explain the abnormal behavior of alkoxyalkyl esters in the aldol condensation, should also strongly favor exclusive formation of intermediate **12**. This high stereoselectivity was lost under conditions that do not favor formation of stable metal chelates (Expt. 2): condensation of the ammonium enolate of **4***b* to acetaldehyde was found to be much slower, giving only 33% of a 1:1 mixture of the two *trans* aldols **8***b* and **9***b* after 15 min. This clearly shows that metal chelation provides not only stereochemical control but also reduces the energy barrier to the condensation products.

In the presence of a sterically important substituent on the nitrogen atom (Expt. 3) *trans*/*cis* stereoselectivity was greatly reduced. On the one hand, one could reason that steric interference between the bulky groups at positions 1 and 4 of azetidinone **4***c* would increase the relative population of the α-face N-substituent with the consequence that the C-4α proton is no longer the only important interaction-maker at the α-face. As a result transition states **14** and **15** are not destabilized, relative to **12** and **13**, to the same extent and the proportion of *cis* product is increased accordingly (*trans*/*cis* = 7:3). On the other hand, azetidinone **17** (14), with a smaller size substituent at position 4, was reported to give a *trans*/*cis* ratio of 83:16, which indicates that the presence of a sulfur atom at position 4 of azetidinone **4***c* is partly responsible for the lowered *trans*/*cis*



SCHEME 3

ratio observed with **4***c*. Possibly, under conditions of kinetic control, chelation to sulfur (18), as depicted in **18**, would facilitate β-face approach and favor transition to **14** and **15**. This effect was not noted with **4***b* because of the greater propensity of oxygen to chelate with metals. In such a hypothesis enhancement of the chelating properties of the cationic center would strengthen chelation to sulfur and increase the proportion of attack to the more hindered β-face; indeed replacing lithium by the divalent magnesium (19) gave a *trans*/*cis* ratio approaching unity (Expts. 4 and 6).

Little change in the *trans*/*cis* ratio was observed when THF was replaced by a less polar solvent (Expts. 3 and 4) or when the condensation was carried under conditions likely to permit thermodynamic equilibration (Expt. 5). It is interesting to note that the highly abnormal *cis R**/*cis S** < 1 ratio in THF (Expt. 3) changed, in ether (Expt. 4), to a ratio that is more in line with nonbonded interactions in **14** and **15**.

Attempts to disrupt the organized transition state from **4***c* were unsuccessful. Use of the highly dissociating solvent HMPT (9*b*) led to the discovery of a mild deprotection reaction for N-silyl protected azetidinones:[5] solution of **4***c* in HMPT (or DMF), in the presence of a nucleophile (diisopropylamine from LDA, NaN_3,...) at low temperature afforded a quantitative yield of **4***a*. Attempts to generate the ammonium enolate with tetrabutylammonium fluoride also resulted in protecting group removal (the corresponding bromide and iodide were completely insoluble in THF at −78°C and did not bring any change in the *trans*/*cis* ratio). The ammonium enolate could have possibly been obtained by treatment of the O-trimethylsilyl enol ether of **4***c* with an equivalent of tetrabutylammonium fluoride; treatment of the lithium enolate of **4***c* with trimethylsilyl chloride not unexpectedly (20, 21) afforded only the C-silylation product **19**.[6]

In summary, the stereochemistry of aldol condensation products of 4-tritylthioazetidinones with acetaldehyde varied according to the type and size of the nitrogen protecting group, with minimal effect from solvent or reaction conditions. The strength of the chelation of the metal cation, not only with the enolized carbonyl group itself but also with other electronegative groups, on the azetidinone was found to be an important factor in the stereochemical control of the reaction. The four possible isomers of **6** were obtained but neither the methoxymethyl nor the *tert*-butyldimethylsilyl protecting groups provided the "natural" isomers of **6** as major products. Stereoselective conversion of **4** to "natural" **6** will make the object of a forthcoming publication.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are not corrected. The infrared spectra were recorded on a Perkin−Elmer 267 grating infrared spectrophotometer.

The ^1H nuclear magnetic resonance data were taken with either a Varian EM-360A (60 MHz) or a Varian CFT-20 (80 MHz) nmr spectrometer using tetramethylsilane as an internal standard. The analyses were performed by Micro-Tech Laboratories, Skokie, Illinois and Daessle Microanalysis, Montréal, Que.

Tetrahydrofuran was freshly distilled from $LiAlH_4$. Anhydrous ether (Mallinckrodt) and *n*-butyllithium in hexane (Aldrich) were used as supplied. Commercial CH_3CHO was distilled prior to use. Diisopropylamine was distilled from CaH_2 and stored over NaOH.

1-Methoxymethyl-4-tritylthio-2-azetidinone (4b)

A solution of 4-tritylthio-2-azetidinone (**4***a*) (1.38 g, 4.0 mmol) in THF (10 mL) was added to a well stirred suspension of sodium hydride (300 mg of commercial 50% oil dispersion, 4.1 mmol, washed with pentane) in THF (10 mL) maintained at −15°C (ice−methanol bath). Methanol (15 drops) was added and the mixture was stirred at −15°C for 0.5 h. Bromomethyl methyl ether (0.58 g, 4.6 mmol) was added, the mixture was stirred for 2 h, diluted with ether, washed with water and brine, dried ($MgSO_4$), and concentrated to leave an oil (1.72 g). Crystallization from pentane gave the title compound **4***b* as a white solid (1.41 g, 3.64 mmol, yield: 91%), mp 72−76°C; ir (CH_2Cl_2) ν_{max}: 1765 (β-lactam C=O) cm^{-1}; ^1Hmr ($CDCl_3$) δ: 7.4−7.2 (15H, m, aromatic H), 4.6−4.37 (H-4), 4.43 (2H, center of ABq, CH_2), 3.25 (3H, s, CH_3), 2.93 (1H, dd, J = 15.4, J = 4.1, H-3), 2.68 (1H, dd, J = 15.4, J = 3.4, H-3). *Anal.* calcd. for $C_{24}H_{23}NO_2S$: C 74.00, H 5.95, N 3.59, S 8.23; found: C 73.97, H 6.02, N 3.74, S 8.20.

*1-(*tert*-Butyldimethylsilyl)-4-tritylthio-2-azetidinone (4c)*

Triethylamine (1.62 mL, 11.6 mmol) was added dropwise in 5 min to a cooled (ice bath) solution of 4-tritylthio-2-azetidinone (**4***a*) (3.50 g, 10.1 mmol) and *tert*-butyldimethylsilyl chloride (1.68 g,

[6]Use of **19** as starting material for new C-3 substituted azetidinones will make the object of a subsequent paper.

TABLE 3. Analytical data for **8***c*, **9***c*, **10***c*, **11***c*

Compound	Melting point, 0°C	Infrared ($CHCl_3$) ν_{max}, cm^{-1} OH	C=O	*Anal.* for $C_{30}H_{37}NO_2SSi$ Calcd.	Found
8*c*	134–136	3580 (w) 3560–3200 (m)	1735 (s)	C 71.52 H 7.40 N 2.78 S 6.36	71.30 7.41 2.55 6.30
9*c*	158–159	3560 (m) 3500–3300 (w)	1745 (s)	C Idem H Idem N Idem S Idem	71.50 7.51 2.60 6.46
10*c*	171–172	3540–3300 (m)	1745 (s)	C Idem H Idem N Idem S Idem	71.27 7.43 2.51 6.31
11*c*	152–153	3550 (m) 3500–3300 (w)	1735 (s)	C Idem H Idem N Idem S Idem	71.28 7.41 2.48 6.19

12.7 mmol) in DMF (35 mL). The reaction mixture was stirred at room temperature for 18 h, diluted with water (250 mL) and ether (200 mL), the organic phase washed with water (3 × 50 mL), dried, and concentrated to leave an oil (4.33 g). Crystallization from pentane gave the title compound **4***c* as a white solid (4.1 g, 8.9 mmol, yield: 89%), mp 113–114°C; ir (CH_2Cl_2) ν_{max}: 1735 (β-laetam C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 7.8–7.2 (15H, m, aromatic H), 4.2 (1H, dd, J = 4, J = 2, H-4), 2.63 (1H, dd, J = 16, J = 4, H-3), 2.13 (1H, dd, J = 16, J = 2, H-3), 1.0 (9H, s, *t*-Bu), 0.35 (6H, s, CH_3). *Anal.* calcd. for $C_{28}H_{33}NOSSi$: C 73.15, H 7.24, N 3.05, S 6.97; found: C 73.27, H 7.32, N 2.97, S 6.94.

trans S* *3-(1'-hydroxyethyl)-1-methoxymethyl-4-tritylthio-2-azetidinone* (*8*b)

A solution of lithium diisopropylamide was prepared in THF (5 mL) at low temperature (Dry Ice – acetone bath) from *n*-butyllithium (1.0 mL, 1.6 *M* in hexane, 1.6 mmol) and diisopropylamine (0.25 mL, 1.84 mmol). After 30 min a solution of 1-methoxymethyl-4-tritylthio-2-azetidinone (**4***b*) (421 mg, 1.42 mmol) in THF (6 mL) was added dropwise and the solution was stirred for 15 min. Acetaldehyde (3 mL) ws added dropwise followed, after 20 min, by water (30 mL). The mixture was acidified to pH 3 with 2% aqueous HCl and extracted with ethyl acetate (5 × 20 mL). The combined organic phases were washed with brine, dried, and concentrated to leave an oil which crystallized upon trituration with ether (440 mg, 1.01 mmol, yield: 80%) mp 188.5–189°C; ir (CH_2Cl_2) ν_{max}: 3610 (m, OH), 1755 (s, β-lactam C=O) cm^{-1}. *Anal.* calcd. for $C_{26}H_{27}NO_3S$: C 72.02, H 6.28, N 3.23, S 7.39; found: C 71.94, H 6.02, N 3.21, S 7.40.

trans S* *and* R* *3-(1'-hydroxyethyl)-1-methoxymethyl-4-tritylthio-2-azetidinones* (*8*b *and* *9*b)

A solution of lithium diisopropylamide (0.482 mmol) was prepared at −78°C (Dry Ice – acetone bath) in dry ether (3 mL) from *n*-butyllithium (0.101 mL, 2.52 *M* in hexane, 0.482 mmol) and diisopropylamine (0.067 mL, 0.482 mmol). After 20 min, a solution of azetidinone **4***b* (0.171 g, 0.439 mmol) in a mixture of dry ether (1 mL) and THF (1 mL) was added dropwise and the resulting clear solution was stirred at −78°C for 15 min. A solution of tetrabutylammonium fluoride (0.96 mL of a 0.5 *M* solution in THF, 0.48 mmol) was then added. A precipitate was formed with the generation of a slight pink colour. After 5 min at −78°C, the reaction mixture was quenched with acetaldehyde (0.2 mL, excess), and the stirring continued for 15 more min. A saturated solution of NH_4Cl was added and the mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic phases were washed with brine and dried ($MgSO_4$) and concentrated to leave an oil (228 mg). This was chromatographed on silica gel (10 g), using a mixture of benzene and ethyl acetate (6:4) to give back substrate (**4***b*) (106 mg, 62% recovery) and a mixture of two isomeric alcohols which were separated by chromatography on thick layer plates (same solvent system). The alcohol with high R_f (33 mg, 0.076 mmol, yield: 17%) was identical to **8***b*, mp 188.5–189.5°C. The alcohol with low R_f (30 mg, 0.069 mmol, yield: 16%) was obtained as an oil which crystallized with difficulty (hexane), mp 94–95°C; ir (CH_2Cl_2) ν_{max}: 3600 (m, OH), 1760 β-lactam C=O) cm^{-1}. *Anal.* calcd. for $C_{26}H_{27}NO_3S$: C 72.02, H 6.28, N 3.23, S 7.39; found: C 71.77, H 6.36, N 3.15, S 7.43.

trans S* *and* R* *and* cis R* *and* S* *1-(*tert*-*butyldimethylsilyl*)-*3-(1'-hydroxyethyl)-4-tritylthio-2-azetidinone* (*8*c, *9*c, *10*c, *11*c)

1. *In THF*

To a solution of diisopropylamine (15.0 mL, 10.8 g, 0.107 mmol) in THF (450 mL) maintained at −78°C was added dropwise *n*-butyllithium (42.0 mL, 2.22 *M* in hexane, 0.093 mmol). The mixture was stirred for 30 min and a solution of **4***c* (30.0 g, 65.4 mmol) in THF (250 mL) was added slowly. After 15 min stirring, acetaldehyde (35 mL, excess) was added in one portion. The reaction mixture was allowed to react 15 more min, poured on saturated aqueous NH_4Cl solution (1 L), and acidified to pH 2 with 10% aqueous HCl. The aqueous phase was extracted with ethyl acetate (3 × 500 mL). The organic phases were combined, washed with brine (1 × 500 mL), dried (Na_2SO_4), and concentrated to leave an oil which was found to consist of a mixture of 4 isomers with respective R_f on silica gel MO6F (benzene/ether, 3:1): **8***c*, 0.4; **9***c*, 0.3; **10***c*, 0.5; **11***c*, 0.22. The isomeric ratio was determined on a Waters Associates Prepak-500-Silica column (see Table 1). The same reaction was repeated on **4***c* (294 g, 0.640 mol). Crystallization of the oily residue in petroleum ether 30–60°C after work-up gave a mixture of isomers **8***c* and **9***c* as a white solid. The mother liquor was found to contain mainly isomers **10***c* and **11***c*. All four isomers were then separated by hplc to give title compounds (296.8 g, 0.589 mol) in 92% combined yield.

2. *In ether*

n-Butyllithium (15.6 mL, 1.6 *M* in hexane, 25 mmol) was added dropwise to a solution of diisopropylamine (4.0 mL, 28 mmol) in ether (150 mL) maintained at −78°C (Dry Ice – acetone bath). After 0.5 h a solution of **4***c* (9.2 g, 20 mmol) in ether (100 mL) was added dropwise; after 15 min acetaldehyde (30 mL) was added in one portion. After 1 min an aliquot (10 mL) was quenched with saturated aqueous NH_4Cl and worked up according to the above procedure (see Table 1 for the isomeric ratio). Another aliquot (10 mL) was allowed to warm up to 20°C, stirred for a 2 h period, worked up, and the isomeric ratio determined by hplc (see Table 1).

3. *With the magnesium enolate*

A solution of LDA prepared at −20°C (Dry Ice − CCl_4) from *n*-butyllithium (0.22 mL, 2.52 *M* in hexane, 0.55 mmol) and diisopropylamine (0.077 mL, 0.055 mmol) in THF (3 mL) was stirred for 15 min and cooled at −78°C. It was treated with 1-(*tert*-butyldimethylsilyl)-4-tritylthio-2-azetidinone (230 mg, 0.50 mmol). After 15 min stirring at −78°C the solution was treated dropwise with a solution of $MgBr_2$ in ether (0.224 mL, 2.45 *M*, 0.55 mmol). A precipitate was formed and the mixture was warmed in a CCl_4 − Dry Ice bath for 1 min to solubilize the solid. The clear solution was cooled again (Dry Ice − acetone bath) and acetaldehyde (0.2 mL) was added in one portion. The mixture was stirred for 15 min and worked up as above (see Table 1 for the proportion of isomers).

trans-*1-(*tert-*Butyldimethylsilyl)-3-trimethylsilyl-4-tritylthio-2-azetidinone (**19**)*

A solution of lithium diisopropylamide (25.6 mmol) was prepared at −78°C in THF (120 mL) from diisopropylamine (3.58 mL, 25.6 mmol) and *n*-butyllithium (10.1 mL, 2.52 *M* in hexane, 25.6 mmol). After 30 min at −78°C, a solution of 1-(*tert*-butyldimethylsilyl)-3-tritylthio-2-azetidinone (11.2 g, 24.4 mmol) in THF (25 mL) was added dropwise, followed after 10 min by a solution of trimethylsilyl chloride (2.78 g, 25.6 mmol) in THF (5 mL) containing a few drops (2−3) of triethylamine. After 10 min at −78°C, the clear mixture was poured onto a solution of saturated ammonium chloride (200 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to leave a white solid which was recrystallized from a mixture dichloromethane−hexanes to give white cubes (11.7 g, 22.0 mmol, yield: 90%), mp 157−158°C; ir (KBr disk) ν_{max}: 1742 (s, β-lactam C=O), 840 (C—Si) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 7.9−7.3 (m, 15H, aromatics), 3.84 (d, 1H, *J* = 1.7, H-4), 3.21 (d, 1H, *J* = 1.7, H-3), 0.88 (s, 9H, *t*-Bu), 0.04 and −0.06 (2s, 2 × 3H, $Si(CH_3)_2$), −0.20 (s, 9H, $Si(CH_3)_3$). *Anal.* calcd. for $C_{31}H_{41}NOSSi_2$: C 70.00, H 7.77, N 2.63, S 6.03; found: C 70.25, H 7.91, N 2.65, S 6.10.

Acknowledgements

We would like to thank Drs. Y. Ueda and E. Ruediger for helpful discussions during the preparation of this manuscript. We also thank Messrs. G. Lacasse and P. Rivest for 80 MHz ^{1}Hmr spectra during the course of this work.

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