An Approach to Clavams and 1-Oxacephams from Hydroxy Acids

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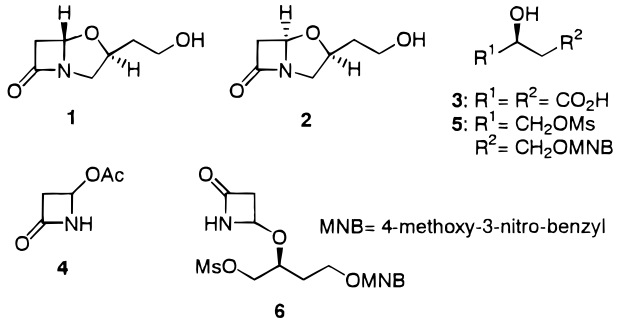
[2 + 2] Cycloaddition of chlorosulfonyl isocyanate to chiral alkyl vinyl ethers bearing a sterogenic center in the alkyl part of the ether afford the corresponding azetidin-2-ones with relatively good asymmetric induction in certain cases. Reactions were shown to depend on steric requirements of the ligands at the stereogenic center. The model that rationalizes the stereochemical outcome is based on the *s-cis* conformation of the vinyl ether in which the bulkiest of the ligands is situated in the plane of the double bond, and the next most demanding substituent is placed gauche to the double bond.

Introduction

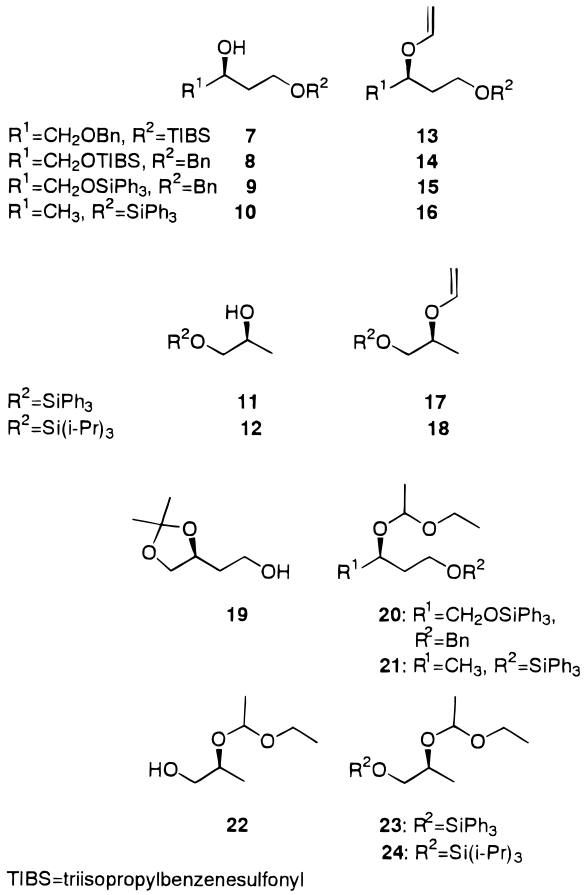
Recently Hoppe and Hilpert[1] have reported on the stereoselective total synthesis of (−)-(2*S*,5*S*)-2-(2′-hydroxyethyl)clavam (**1**)[2] and its (+)-(2*S*,5*R*)-epimer (**2**) from (*S*)-malic acid (**3**). The crucial step of the synthesis was based on enantioselective condensation of 4-acetoxyazetidin-2-one (**4**) with a 1,4-disubstituted derivative of (*S*)-1,2,4-butanetriol (**5**) to afford 4-alkoxyazetidin-2-one **6** as a mixture of 4(*S*) and 4(*R*) epimers in a ratio of 5:6, respectively.



Coupling of **4** with a variety of chiral alcohols, which has been commonly used for clavam construction,[1,3] usually gives low asymmetric induction. Very recently we have developed an alternative methodology consisting of [2 + 2]cycloaddition of chlorosulfonyl isocyanate to sugar vinyl ethers.[4,5] These reactions have been shown to depend on steric factors and have displayed, in many cases, excellent diastereoselectivity. It was of interest to examine this concept using the simple chiral alkyl vinyl ethers **13**−**18** having a stereogenic center in the alkyl part of the ether. We expected to obtain some information regarding the influence of the substituents at the stereogenic center on facial differentiation during [2 + 2]cycloaddition and to propose a stereochemical model of this reaction. The products of cycloaddition might serve for construction of clavam and 1-oxacepham skeletons *via* intramolecular cyclization.

Results and Discussion

1,4-Di-*O*-substituted butene-1,2,4-triols **7**−**9** were synthesized from the common precursor **19**[6] obtained from dimethyl (*S*)-malate, whereas alcohols **10**−**12** were obtained by reduction of the methoxycarbonyl function in methyl (*R*)-3-hydroxybutyrate and methyl (*S*)-lactate, respectively, followed by suitable protection of the primary hydroxymethyl group. A known mercury acetate-catalyzed transetherification method[7] transformed compounds **7** and **8** into the corresponding vinyl ethers **13** and **14**. Since we have observed migration of the triphenylsilyl substituent in the presence of mercury acetate,[4] compounds **15**−**18** were obtained from the corresponding alcohols **9**−**12** by a two-step procedure involving formation of acetals **20**−**24** following by TMS-triflate-catalyzed elimination of ethanol.[8]



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(1) Hoppe, D.; Hilpert, T. *Tetrahedron* **1987**, *43*, 2467−2474.
(2) Wanning, M.; Zähner, H.; Krone, B.; Zeeck, A. *Tetrahedron Lett.* **1981**, *22*, 2539−2540.
(3) Müller, J. C.; Toome, V.; Pruess, D. L.; Blount, J. F.; Weigele, M. *J. Antibiot.* **1983**, *36*, 217−225. De Bernardo, S.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3457−3462.
(4) Kałuża, Z.; Furman, B.; Patel, M.; Chmielewski, M. *Tetrahedron Asymmetry* **1994**, *5*, 2179−2186.
(5) Kałuża, Z.; Furman, B.; Chmielewski, M. *Tetrahedron Asymmetry* **1995**, *7*, 1719−1730.

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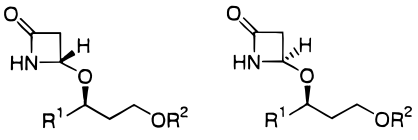
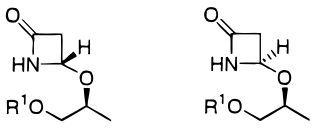
[2 + 2] Cycloaddition of chlorosulfonyl isocyanate to vinyl ethers **13**−**18** was performed in toluene solution at −78 °C in the presence of sodium carbonate as the acid scavenger.[9] The chlorosulfonyl group was removed from the nitrogen atom of the adduct by Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride) reduction.[10] The absolute configurations at C-4′ of azetidinones **25**−**48** were established by comparison to the configuration of the corresponding 1-oxacephams **49**, **50**, **53**, **54** and clavams **51**, **52**, **55**, **56** obtained by intramolecular alkylation of **25**−**48**.



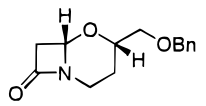
R^1= CH_2OBn, R^2= TIBS	**25**	d.e. 0%	**26**	
R^1= CH_2OTIBS, R^2= Bn	**27**	d.e. 40%	**28**	
R^1= CH_2OSiPh_3, R^2=Bn	**29**	d.e. 65%	**30**	
R^1= CH_2OH, R^2= Bn	**31**		**32**	
R^1= CH_2OTs, R^2= Bn	**33**		**34**	
R^1= CH_3, R^2= $SiPh_3$	**35**		**36**	d.e. 45%
R^1= CH_3, R^2= H	**37**		**38**	
R^1= CH_3, R^2= Ts	**39**		**40**	



R^1= $SiPh_3$	**41**	d.e. 74%	**42**
R^1= $Si(i\text{-}Pr)_3$	**43**	d.e. 69%	**44**
R^1= H	**45**		**46**
R^1= Ts	**47**		**48**

A mixture of compounds **25** and **26** subjected to cyclization afforded cephams **49** and **50** in a ratio of 1:1, which were separated by chromatography into pure components. The configuration of both cephams **49** and **50** was proved by ^{1}H NMR. An NOE experiment on **49** showed strong cross-relaxation between the H-2 and H-6 protons. Irradiation of the signal due to H-2 (δ 4.19) was found to enhance the intensity of the signal due to H-6 (δ 5.18) by 7.1%. Conversely, the signal due to H-2 was enhanced by 6.2% when H-6 was irradiated. In the case of **50**, NOE interactions between H-2 (δ 3.82) and H-6 (δ 4.98) were not observed. These findings testified to a (2*S*,6*S*) configuration for **49** and (2*S*,6*R*) for **50**.

A mixture of compounds **27** and **28** after cyclization provided clavams **51** and **52** in a ratio of 7:3, respectively, which were nonseparable by chromatography.[1] A mixture of **29** and **30** obtained from **15** was transformed into **33** and **34** which were in turn cyclized to afford clavams **51** and **52** in a ratio of 5:1, respectively. A similar sequence of reactions transformed the mixture of **35** and **36** into cephams **53** and **54** in a ratio of 1:3, respectively,



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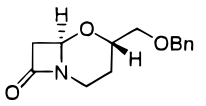

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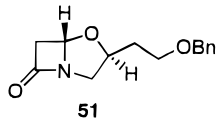

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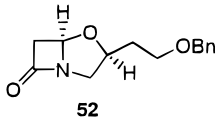

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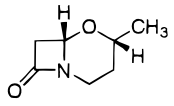

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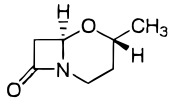

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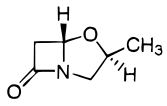

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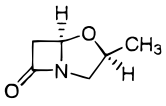

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and the mixture of **41** and **42** into clavams **55** and **56** in a ratio of 6.7:1, respectively. NOE experiments performed on the major components of diastereomeric mixtures **51**/**52**, **53**/**54** and **55**/**56** did not show any spin interactions between H-2 and the bridgehead proton thus proving (2*S*,5*S*) configuration for clavams **51** and **55** and (2*R*,6*R*) for cepham **54**.

Vinyl ether **13** afforded diastereomers **25** and **26** in a ratio of about 1:1. Compound **14**, which has TIBS and benzyl substituents interchanged as compared to **13**, gave **27** with 40% diastereomeric excess. Replacement of the TIBS group in **14** by the more bulky triphenylsilyl substituent improved facial differentiation to afford **29** with 65% de; compound **16** yielded β-lactam **36** with 45% de. It should be stressed that the direction of asymmetric induction in the case of **16** was reversed compared to addition to **14** and **15**. Compounds **17** and **18** having bulky silyl substituents next to the stereogenic center produced respective azetidinones **41** with 74% de and **43** with 69% de.

The results of asymmetric induction of [2 + 2] cycloaddition of chlorosulfonyl isocyanate to vinyl ethers **13**−**18** testify to the steric control of the reaction. The direction and magnitude of the asymmetric induction depend on the steric requirements of both alkyl ligands attached to the stereogenic center. If the alkyl ligands do not differ significantly in size, stereoselectivity is low; for example, compounds **13**, **14**, and **16**. Increasing the size of the 1-*O*-substituent in the sequence: benzyl, TIBS, triphenylsilyl causes an increase in stereoselectivity. The same tendency can be found if stereoselectivity of addition to **15** and **17** is compared. The higher induction found for **17** versus **15** is caused by reduction in size of the alkyl group: benzyloxyethyl versus methyl.

Recently published *ab initio* calculations of conformational energies of isopropyl vinyl ether reported the *synclinal s-cis* conformation **57** as the most stable one.[11] Application of the conformation **57**, having the siloxyl, benzyloxyl, or sulfonyloxyl oxygen atom located *antiperiplanar* to the vinyloxy oxygen atom, could explain the direction of stereoselectivity: the diastereo-zeroplane is supposed to consist of the vinyl group, the stereogenic center, and the R_L substituent. Diastereofacial differentiation in such a stereochemical model is related to

(6) Corey, E. J.; Niwo, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942−1943. Mulzer, J.; De Lasalle, P. *J. Chem. Res. (S)*, **1983**, 10−11.

(7) Watanable, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828−2833.

(8) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653−1656.

(9) Chmielewski, M.; Kałuża, Z.; Abramski, W.; Bełżecki, C.; Grodner, J.; Mostowicz, D.; Urbański, R. *Synlett.* **1994**, 539−541.

(10) Hungerbühler, E.; Bialoz, M.; Ernest, F.; Kalvoda, J.; Langa, M.; Schneider, P.; Sedelmeier, G. In *New Aspects of Organic Chemistry*; Yoshida, Z., Shiba, T., Oshiro, Y., Eds.; VCH: New York, 1989; pp 419−451.

(11) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensery, A. *J. Org. Chem.* **1995**, *60*, 3205−3220.

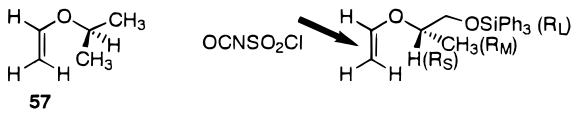

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Figure 1.

atomic requirements of the methyl group (R_M) versus the hydrogen atom R_S (Figure 1). The isocyanate approaches the double bond from the R_S(H) side. If, however, the R_L and R_M substituents do not differ greatly in steric requirements (for example in compounds **13**, **14**, **16**) the diastereodifferentation is low.

Our investigation has shown that [2 + 2] cycloaddition of chlorosulfonyl isocyanate to simple chiral vinyl ethers bearing a stereogenic center in the alkyl part of the ether can provide relatively good asymmetric induction in certain cases, better than that found in the alternative method involving condensation of 4-acetoxyazetidin-2-one (**4**) with the corresponding alcohols.[1] The observed stereoselectivity testifies to a defined geometry of the transition state. The stereochemical model which uses conformation **57** (Figure 1) might explain the experimental results although we have not observed direct evidence to suport the model. It should be noted that cyclic chiral vinyl ethers (glycals) offered better asymmetric induction in [2 + 2] cycloaddition with isocyanates.[13]

Experimental Section

Column chromatography was perfomed on Merck Kieselgel (230−400 mesh). Compound **19** was obtained according to ref 6, whereas **22** was obtained according to ref 12.

(*S*)-1-*O*-Benzyl-4-*O*-(triisopropylbenzenesulfonyl)-1,2,4-butanetriol (7), (*S*)-4-*O*-benzyl-1-*O*-(triisopropylbenzenesulfonyl)-1,2,4-butanetriol (8), and (*S*)-4-*O*-benzyl-1-*O*-(triphenylsilyl)-1,2,4-butanetriol (9) were obtained from **17**[6] using standard sequences of reactions involving benzylation or sulfonylation, followed by hydrolysis of the isopropylidene grouping, and subsequent respective standard sulfonylation, benzylation, or silylation.

7: $[\alpha]_D = -7.3°$ (*c* 1.2, CH_2Cl_2); IR ($CHCl_3$) 3580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24, 1.27 (2s, 18H), 1.70−1.98 (m, 2H), 2.85 (sept, 1H), 3.36 (dd, 1H, J = 7.3, 9.4 Hz), 3.50 (dd, 1H, J = 3.3, 9.4 Hz), 3.98 (m, 1H), 4.18 (sept, 2H), 4.08−4.32 (m, 2H), 4.54 (s, 2H); MS (EI, HR) m/z (M^+) calcd 462.24399, obsd 462.24377. Anal. Calcd for $C_{26}H_{38}O_5S$: C, 67.50; H, 8.28; S, 6.93. Found: C, 67.53; H, 8.37; S, 6.89.

8: $[\alpha]_D = -5.0°$ (*c* 0.98, CH_2Cl_2); IR ($CHCl_3$) 3498 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24, 1.27 (2s, 18H), 1.69−1.92 (m, 2H), 2.91 (sept, 1H), 3.57−3.78 (m, 2H), 3.92−4.16 (m, 3H), 4.13 (m, 2H), 4.50 (s, 2H); MS (EI, HR) m/z (M^+) calcd 462.24399, obsd 462.24377. Anal. Calcd for $C_{26}H_{38}O_5S$: C, 67.50; H, 8.28; S, 6.93. Found: C, 67.62; H, 8.20; S, 7.02.

9: $[\alpha]_D = -0.55°$ (*c* 1.5, CH_2Cl_2); IR ($CHCl_3$) 3531 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67−1.87 (m, 2H), 3.52−3.83 (m, 4H), 3.95 (m, 1H), 4.46 (s, 2H); MS (HR, LSIMS) m/z (M + Na)$^+$ calcd 477.186985, obsd 477.18632. Anal. Calcd for $C_{29}H_{30}O_3Si$: C, 76.61; H, 6.65. Found: C, 76.44; H, 6.63.

(3*R*)-1-*O*-(Triphenylsilyl)butane-1,3-diol (10). Compound **10** was obtained from commercially available butane-1,3-diol *via* standard silylation with triphenylsilyl chloride (70%): $[\alpha]_D = -2.4°$ (*c* 1.4, CH_2Cl_2); IR ($CHCl_3$) 3507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, 3H), 1.60−1.85 (m, 2H), 3.90−4.15 (m, 3H); MS (HR, LSIMS) m/z (M + H)$^+$ calcd 349.16238, obsd 349.163026. Anal. Calcd for $C_{22}H_{24}O_2Si$: C, 75.82; H, 6.94. Found: C, 75.70; H, 6.85.

(*S*)-1-*O*-Benzyl-2-*O*-vinyl-4-*O*-(triisopropylbenzenesulfonyl)butane-1,2,4-triol (13). A solution of **7** (0.46 g, 1 mmol) and mercury acetate (0.03 g) in *n*-butyl vinyl ether (15 mL) was refluxed for 6 h. Subsequently solvent was evaporated, and the remaining syrup was purified on a silica gel column using hexane *tert*-butyl methyl ether 95:5 v/v as an eluent to afford **13** (0.3 g, 62%): $[\alpha]_D = -6.7°$ (*c* 0.30, CH_2Cl_2); IR (film) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23, 1.24, 1.26, 1.27 (4s, 18H), 1.90−2.15 (m, 2H), 2.91 (sept, 1H), 3.44−3.64 (m, 2H), 4.00 (dd, 1H, J = 1.8, 6.6 Hz), 4.02−4.22 (m, 5H), 4.30 (dd, 1H, J = 1.8, 14.1 Hz), 4.53 (s, 2H), 6.28 (dd, 1H, J = 6.6, 14.1 Hz); MS (HR, LSIMS) m/z (M^+ + H) calcd 489.26747, obsd 489.2673. Anal. Calcd for $C_{28}H_{40}O_5S$: C, 68.85; H, 8.20; S, 6.56. Found: C, 68.40; H, 8.10; S, 6.28.

(*S*)-4-*O*-Benzyl-2-*O*-vinyl-1-*O*-(triisopropylbenzenesulfonyl)butane-1,2,4-triol (14). Compound **14** was obtained from **8** according to the procedure described above (56%): $[\alpha]_D = -17.8°$ (*c* 0.50, CH_2Cl_2); IR (film) 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24, 1.27 (2s, 18H), 1.88 (m, 1H), 2.91 (sept, 1H), 3.54 (t, 2H), 3.96 (dd, 1H, J = 1.8, 6.6 Hz), 4.03−4.32 (m, 5H), 4.25 (dd, 1H, J = 1.8, 14.0 Hz), 4.46 (s, 2H), 6.22 (dd, 1H, J = 6.6, 14.0 Hz); MS (HR, LSIMS) m/z (M + Na)$^+$ calcd 511.24802, obsd 511.2473.

(2*S*)-4-*O*-Benzyl-2-*O*-(1′-ethoxyethyl-1-*O*-(triphenylsilyl)butane-1,2,4-triol (20). A solution of alcohol **9** (1.00 g, 2.2 mmol) in ethyl vinyl ether (4 mL) was cooled to 0 °C and treated with trifluoroacetic acid (1 μL). The mixture was left at rt until disappearance of the substrate (4 days). Subsequently, upon stirring, pulverized sodium carbonate (0.10 g) was added. After 1 h the inorganics were filtered, and the ether was evaporated. The crude product was purified on a silica gel column using hexane: *tert*-butyl methyl ether 9:1 v/v as eluent to afford **20** as a 1:1 diastereomeric mixture (1.01 g, 94%): IR (film) 1436 cm^{-1}; ^1H NMR ($CDCl_3$) δ *inter alia* 1.01, 1.11 (2t, 3H), 1.21, 1.24 (2d, 3H), 4.63, 4.79 (2q, 1H); MS (HR, LSIMS) m/z (M + H)$^+$ calcd 527.26176, obsd 527.2619. Anal. Calcd for $C_{33}H_{38}O_4Si$: C, 75.25; H, 7.27. Found: C, 75.10; H, 7.15.

(3*R*)-3-*O*-(1′-Ethoxyethyl)-1-*O*-(triphenylsilyl)butane-1,3-diol (21). Compound **21** was obtained according to the procedure described for **20** (99%): IR (film) 1117, 1429 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals of acetal proton of two diastereomers 4.60, 4.71 (2q, 1H, J = 5.3 Hz); MS (HR, LSIMS) m/z (M + Na)$^+$ calcd 443.201843, obsd 443.2018. Anal. Calcd for $C_{26}H_{32}O_3Si$: C, 72.28; H, 7.62. Found: C, 72.10; H, 7.46.

(2*S*)-2-*O*-(1′-Ethoxyethyl)-1-*O*-(triphenylsilyl)propane-1,2-diol (23). Compound **22** (4.86 g, 33 mmol) dissolved in dry pyridine (40 mL) was cooled to 0 °C and treated with triphenylsilyl chloride (10.33 g, 35 mmol). The temperature of reaction was allowed to rise to rt, and the mixture was left for 3 h, until disappearance of the substrate (TLC). Subsequently, the solution was poured into ice−water (200 mL) and extracted with *tert*-butyl methyl ether (3 × 50 mL). Combined extracts were dried and evaporated. The crude product was purified by chromatography to afford **23** (13.0 g, 96%): IR (film) 1171, 1429 cm^{-1}; ^1H NMR ($CDCl_3$) δ *inter alia* 1.07, 1.15 (2t, 3H), 1.16, 1.18 (2d, 3H), 1.26 (d, 1H), 4.74, 4.80 (2q, 1H); MS (HR, LSIMS) m/z (M + Na)$^+$ calcd 429.186189, obsd 429.186017. Anal. Calcd for $C_{25}H_{30}O_3Si$: C, 73.85; H, 7.44. Found: C, 73.87; H, 7.20.

(2*S*)-2-*O*-(1′-Ethoxyethyl)-1-*O*-(triisopropylsilyl)propane-1,2-diol (24). Compound **24** was obtained according to the procedure described above (85%): IR (film) 1101, 1463 cm^{-1}; ^1H NMR ($CDCl_3$) δ *inter alia* 4.79, 4.88 (2q, 1H); MS (HR, LSIMS) m/z (M + H)$^+$ calcd 305.25119, obsd 305.2513. Anal. Calcd for $C_{16}H_{36}O_3Si$: C, 63.16; H, 11.84. Found: C, 63.22; H, 11.80.

(*S*)-4-*O*-Benzyl-1-*O*-(triphenylsilyl)-2-*O*-vinylbutane-1,2,4-triol (15). A solution of **20** (1.05 g, 2.0 mmol) in CH_2Cl_2 (2 mL) was treated with triethylamine (0.42 mL, 3.0 mmol) under nitrogen. The mixture was stirred and cooled to 0 °C and treated dropwise with TMS-triflate (0.50 mL, 2.6 mmol). Stirring and cooling were continued until disappearance of the substrate (3 h). The mixture was treated with 10% NaOH (1

(12) Hintzer, K.; Koppenhoefer, B.; Schurig, V. *J. Org. Chem.* **1982**, *47*, 3850−3854.

(13) Chmielewski, M.; Kałuża, Z.; Grodner, J.; Urbański, R. In *Cycloaddition Reactions in Carbohydrates*, Giuliano, R., Ed.; ACS Symposium Series 494; American Chemical Society: Washington, DC, 1992; p 50−65. Chmielewski, M.; Kałuża, Z.; Furman, B. *J. Chem. Soc., Chem. Commun.* **1996**, 2689−2696.

mL) and hexane (20 mL). The organic layer was separated, dried, and evaporated. The crude product was purified on a silica gel column using hexane: *tert*-butyl methyl ether 9.5: 0.5 v/v as eluent to give **15** (0.8 g, 83%): $[\alpha]_D = -15.5°$ (*c* 0.5, CH_2Cl_2): IR (film) 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73−2.05 (m, 2H), 3.45−3.62 (m, 2H), 3.83 (d, 2H), 3.91 (dd, 1H, J = 1.5, 6.5 Hz), 4.07 (m, 1H), 4.25 (dd, 1H, J = 1.5, 14.1 Hz), 4.45 (s, 2H), 6.31 (dd, 1H, J = 6.5, 14.1 Hz); MS (HR, LSIMS) m/z (M^+ + Na) calcd 503.20184, obsd 503.2028. Anal. Calcd for $C_{31}H_{32}O_3Si$: C, 77.50; H, 6.67. Found: C, 77.28; H, 6.60.

(*S*)-1-*O*-(Triphenylsilyl)-2-*O*-vinylpropane-1,2-diol (17). Compound **17** was obtained according to the procedure described for **15** (80%): $[\alpha]_D = +1.8°$ (*c* 1.5, CH_2Cl_2); IR (film) 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, 3H, J = 6.3 Hz), 3.71 (dd, 1H, J = 5.2, 10.5 Hz), 3.84 (dd, 1H, J = 5.8, 10.5 Hz), 3.94 (dd, 1H, J = 1.5, 6.5 Hz), 4.02 (sext, 1H), 4.23 (dd, 1H, J = 1.5, 14.1 Hz), 6.31 (dd, 1H, J = 6.5, 14.1 Hz); MS (HR, LSIMS) m/z $(M + Na)^+$ calcd 383.144325, obsd 383.14413.

(*S*)-1-*O*-(Triisopropylsilyl)-2-*O*-vinylpropane-1,2-diol (18). Compound **18** was obtained according to the procedure described for **15** (71%): $[\alpha]_D = +4.3°$ (*c* 0.7, CH_2Cl_2); IR (film) 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, 1H, J = 6.3 Hz), 3.61 (dd, 1H, J = 5.5, 10.1 Hz), 3.77 (dd, 1H, J = 5.7, 10.1 Hz), 3.96 (dd, 1H, J = 1.5, 6.6 Hz), 3.97 (sext, 1H), 4.28 (dd, 1H, J = 1.5, 14.1 Hz), 6.38 (dd, 1H, J = 6.6, 14.1 Hz); MS (HR, LSIMS) m/z $(M + H)^+$ calcd 259.20933, obsd 259.20934. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.12; H, 11.63. Found: C, 64.86; H, 11.60.

(2*S*,4′*S*) and (2*S*,4′*R*) 2-*O*-(2′-Oxoazetidin-4′-yl)-1-*O*-benzyl-4-*O*-(triisopropylbenzenesulfonyl)butane-1,2,4-triol (25 and 26). To a solution of CSI (61 μL, 0.7 mmol) in toluene (1 mL) was added anhydrous Na_2CO_3 (0.08 g). The mixture was cooled to −78 °C and upon stirring was treated dropwise with vinyl ether **13** (0.24 g, 0.5 mmol) in toluene (1 mL). Stirring and cooling were maintained for 1.5 h. The mixture was diluted with toluene (5 mL) and treated at −78 °C with 1 M Red-Al in toluene. After 30 min the mixture was allowed to come to rt, and water (0.4 mL) was added. The mixture was stirred for an additional 30 min, was filtered through Celite and evaporated. Chromatography of on a silica gel column using hexane:ethyl acetate 7:3 v/v as eluent gave a 1:1 mixture of **25** and **26** (0.13 g, 50%): IR ($CHCl_3$) 1769, 3412 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **25** *inter alia* 2.83 (ddd, 1H, J = 0.7, 1.4, 15.0 Hz), 3.08 (ddd, 1H, J = 2.8, 3.9, 15.0 Hz), 5.26 (dd, 1H, J = 1.4, 3.9 Hz); signals due to **26** *inter alia* 2.76 (ddd, 1H, J = 0.9, 1.5, 15.0 Hz), 3.06 (ddd, 1H, J = 2.7, 4.1, 15.0 Hz), 5.04 (dd, 1H, J = 1.5, 4.1 Hz). MS (HR, LSIMS) m/z (M^+ + H) calcd 532.27328, obsd 532.27306.

(2*S*,4′*S*)- and (2*S*,4′*R*)-2-*O*-(2′-Oxoazetidin-4′-yl)-4-*O*-benzyl-1-*O*-(triisopropylbenzenesulfonyl)butane-1,2,4-triol (27 and 28). A mixture of **27** and **28** in a ratio of 7:3, respectively, was obtained from **14** according to the procedure described above (58%). IR ($CHCl_3$) 1772, 3409 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **27** *inter alia* 2.79 (ddd, 1H, J = 0.7, 1.5, 15.2 Hz), 3.05 (ddd, 1H, J = 2.6, 4.0, 15.2 Hz), 5.14 (dd, 1H, J = 1.5, 4.0 Hz); signals due to **28** *inter alia* 2.74 (ddd, 1H, J = 0.9, 1.5, 15.0 Hz), 5.05 (dd, 1H, J = 1.5, 3.9 Hz); MS (EI, HR) m/z (M^+) calcd 531.26545, obsd 531.26540.

(2*S*,4′*S*)- and (2*S*,4′*R*)-2-*O*-(2′-Oxoazetidin-4′-yl)-4-*O*-benzyl-1-*O*-(triphenylsilyl)butane-1,2,4-triol (29 and 30). A mixture of **29** and **30** in a ratio of 4.7:1, respectively, was obtained from **15** according to the procedure described above (56%): IR (film) 1770, 3267 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **29** *inter alia* 2.74 (ddd, 1H, J = 0.8, 1.5, 15.0 Hz), 2.90 (ddd, 1H, J = 2.6, 4.0, 15.0 Hz), 5.14 (dd, 1H, J = 1.5, 4.0 Hz); signals **30** *inter alia* 2.95 (ddd, 1H, J = 2.5, 4.0, 15.0 Hz), 5.03 (dd, 1H, J = 1.5, 4.0 Hz); MS (HR, LSIMS) m/z $(M + H)^+$ calcd 524.226192, obsd 524.2257.

(2*S*,4′*S*) and (2*S*,4′*R*)-2-*O*-(2′-Oxoazetidin-4′-yl)-4-*O*-benzyl-1-*O*-tosylbutane-1,2,4-triol (33 and 34). A solution of a 5:1 mixture of **29** and **30** (0.10 g, 0.20 mmol) in pyridine (1 mL) was treated with HF−pyridine complex (0.026 g, 0.26 mmol). After 2 h tosyl chloride (0.10 g, 0.5 mmol) was added, and the mixture was left overnight in a refrigerator, poured into water, and extracted with *tert*-butyl methyl ether. The extract was dried and evaporated. The crude product was purified on a silica gel column using hexane:ethyl acetate 4:1 v/v as eluent to afford **33** and **34** (81%): IR (film) 1774, 3282 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **33** 1.61, 1.74 (2m, 2H), 2.73 (ddd, 1H, J = 0.7, 1.4, 15.1 Hz), 3.02 (ddd, 1H, J = 2.7, 4.0, 15.1 Hz), 3.49 (m, 1H), 3.60 (dt, 1H), 3.89 (m, 1H), 3.97 (dd, 1H, J = 7.4, 10.5 Hz), 4.06 (dd, 1H, J = 3.0, 10.5 Hz), 4.41, 4.51 (2d, 2H, J = 11.8 Hz), 5.08 (dd, 1H, J = 1.4, 4.0 Hz); signals due to **34** *inter alia* 2.71 (ddd, 1H, J = 0.6, 1.5, 15.0 Hz), 2.98 (ddd, 1H, J = 2.7, 4.0, 15.0 Hz), 5.00 (dd, 1H, J = 1.5, 4.0 Hz); MS (HR, LSIMS) m/z $(M + H)^+$ calcd 420.148092, obsd 420.148085.

(3*R*,4′*S*)- and (3*R*,4′*R*)-3-*O*-(2′-Oxoazetidin-4′-yl)-1-*O*-(triphenylsilyl)butane-1,3-diol (35 and 36). A mixture of compounds **35** and **36** in proportion 1:2.6, respectively, was obtained by addition of CSI to **16** according to the procedure described for addition to **13** (25%): IR (film) 1767, 3257 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **35** *inter alia* 1.15 (d, 1H, J = 6.5 Hz), 2.78 (ddd, 1H, J = 0.7, 1.4, 14.9 Hz), 3.04 (ddd, 1H, J = 2.7, 3.9, 14.9 Hz), 4.99 (dd, 1H, J = 1.5, 2.8 Hz); signals due to **36** *inter alia* 1.17 (d, 1H, J = 6.3 Hz), 2.72 (dd, 1H, J = 0.6, 1.5, 15.0 Hz), 2.94 (dd, 1H, J = 2.9, 4.0, 15.0 Hz), 4.96 (dd, 1H, J = 1.5, 4.0 Hz). MS (HR, LSIMS) m/z $(M + Na)^+$ calcd 440.165788, obsd 440.165753.

(2*S*,4′*S*)- and (2*S*,4′*R*)-2-*O*-(2′-Oxoazetidin-4′-yl)-1-*O*-(triphenylsilyl)propane-1,2-diol (41 and 42). A mixture of compounds **41** and **42** in proportion of 6.7:1, respectively, was obtained by addition of CSI to **17** according to the procedure described for addition to **13** (25%): IR (film) 1769, 3269 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **41** *inter alia* 1.15 (d, 1H, J = 6.2 Hz), 2.77 (ddd, 1H, J = 0.5, 1.5, 15.1 Hz), 2.96 (ddd, 1H, J = 2.9, 3.9, 15.1 Hz), 5.21 (dd, 1H, J = 1.5, 3.9 Hz); signals due to **42** *inter alia* 1.10 (d, 1H, J = 6.4 Hz), 2.79 (ddd, 1H, J = 0.7, 1.5, 15.0 Hz), 3.05 (ddd, 1H, J = 2.8, 4.0, 15.0 Hz), 5.11 (dd, 1H, J = 1.5, 4.0 Hz). MS (HR, LSIMS) m/z (M + H)$^+$ calcd 404.168194, obsd 404.167923.

(2*S*,4′*S*)- and (2*S*,4′*R*)-2-*O*-(2′-Oxoazetidin-4′-yl)-1-*O*-(triisopropylsilyl)propane-1,2-diol (43 and 44). A mixture of compounds **43** and **44** in proportion 5.5:1, respectively, was obtained by addition of CSI to **18** according to the procedure described for addition to **13** (27%): IR (film) 1771, 3263 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **43**, *inter alia* 2.87 (ddd, 1H, J = 0.6, 1.5, 15.0 Hz), 3.11 (ddd, 1H, J = 2.7, 3.9, 15.0 Hz), 5.34 (dd, 1H, J = 1.5, 3.9 Hz); signals due to **44**, *inter alia* 2.83 (ddd, 1H, J = 0.9, 1.5, 15.0 Hz), 5.18 (dd, 1H, J = 1.5, 4.0 Hz). MS (HR, LSIMS) m/z $(M + H)^+$ calcd 302.215147, obsd 302.213864.

(3*R*,4′*S*)- and (3*R*,4′*R*)-3-*O*-(2′-Oxoazetidin-4′-yl)-1-*O*-tosylbutane-1,3-diol (39 and 40). A mixture of compounds **39** and **40** (1:2.7) was obtained from the mixture of **35** and **36** according to the procedure described for **33** and **34** (65%): IR (film) 1770, 3279 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **39** *inter alia* 2.78 (ddd, 1H, J = 0.6, 1.5, 14.9 Hz), 3.11 (ddd, 1H, J = 2.7, 4.0, 14.9 Hz), 4.01 (dt, 1H, J = 4.5, 4.5, 9.9 Hz), 4.26 (dt, 1H, J = 3.5, 9.9, 10.0 Hz), 5.08 (dd, 1H, J = 1.5, 4.0 Hz); signals due to **40** *inter alia* 1.19 (d, 1H, J = 6.2 Hz), 2.46 (s, 1H), 2.74 (ddd, 1H, J = 0.3, 1.5, 15.1 Hz), 3.05 (ddd, 1H, J = 2.9, 4.0, 15.1 Hz), 4.07 (dt, 1H, J = 5.0, 5.0, 9.9 Hz), 4.17 (ddd, 1H, J = 4.6, 9.0, 9.9 Hz), 5.03 (dd, J = 1.5, 4.0 Hz); MS (HR, EI) m/z (M^+) calcd 313.098395, obsd 313.098016.

(2*S*,4′*S*)- and (2*S*,4′*R*)-2-*O*-(2′-Oxoazetidin-4′-yl)-1-*O*-tosylpropane-1,2-diol (47 and 48). A mixture of compounds **47** and **48** (6.7:1) was obtained from the mixture of **41** and **42** according to the procedure described for **33** and **34** (73%): IR (film) 1772, 3266, 3349 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **47** *inter alia* 1.18 (d, 3H, J = 6.3 Hz), 2.46 (s, 3H), 2.77 (ddd, 1H, J = 0.4, 1.5, 15.1 Hz), 3.07 (ddd, 1H, J = 2.9, 3.9, 15.1 Hz), 3.88 (m, 1H), 3.94 (dd, 1H, J = 7.1, 10.5 Hz), 4.00 (dd, 1H, J = 3.5, 10.5 Hz), 5.16 (dd, 1H, J = 1.5, 3.9 Hz); signals due to **48** *inter alia* 1.17 (d, 3H, J = 6.4 Hz), 2.79 (ddd, 1H, J = 0.5, 1.5, 15.1 Hz), 3.10 (ddd, 1H, J = 2.8, 4.0, 15.1 Hz), 5.11 (dd, 1H, J = 1.5, 4.0 Hz); MS (HR, LSIMS) m/z (M + H)$^+$ calcd 300.090565, obsd 300.091288.

(2*S*,6*R*)- and (2*S*,6*S*)-2-[(Benzyloxy)methyl]-1-oxacephams (49 and 50). A mixture of **49** and **50** in a ratio 1:1 was obtained from a mixture of **25** and **26** according to the procedure described earlier (82%).[4,5] Compounds **49** and **50**

were separated on a silica gel column using hexane:ethyl acetate 3:2 v/v as an eluent.

Less polar (TLC) compound **49**: $[\alpha]_D = -24.7°$ (*c* 0.3, CH_2Cl_2); IR (film) 1763, 3497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (m, 1H), 1.98 (m, 1H), 2.79 (dd, J = 0.6, 14.9 Hz), 3.12 (ddd, 1H, J = 1.8, 3.2, 14.9 Hz), 3.19 (m, 1H), 3.69 (dd, 1H, J = 4.9, 10.2 Hz), 3.72 (ddd, 1H, J = 4.0, 13.2 Hz), 3.79 (dd, 1H, J = 6.1, 10.2 Hz), 4.19 (q, 1H), 4.59 (s, 2H), 5.18 (dd, 1H, J = 0.6, 3.2 Hz); MS (EI, HR) *m*/*z* (M^+) calcd 247.12084, obsd 247.120513.

More polar (TLC) compound **50**: $[\alpha]_D = +37.6°$ (*c* 0.2, CH_2Cl_2); IR (film) 1766, 3501 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51−1.57 (m, 2H), 2.87 (dd, J = 0.6, 14.9 Hz), 3.00 (m, 1H), 3.15 (ddd, 1H, J = 1.8, 3.3, 14.9 Hz), 3.45 (dd, 1H, J = 4.2, 10.2 Hz), 3.54 (dd, 1H, J = 6.4, 10.2 Hz), 3.82 (m, 1H), 3.91 (m, 1H), 4.55, 4.61 (2d, 2H, J = 12.2 Hz), 4.98 (dd, 1H, J = 0.6, 3.3 Hz); MS (HR, EI) *m*/*z* $(M + H)^+$ calcd 247.12084, obsd 247.120513.

(2*S*,6*S*)- and (2*S*,6*R*)-2-[2′-(Benzyloxy)ethyl]clavams (51 and 52). A nonseparable mixture of **51** and **52** in a ratio of 7:3, respectively, was obtained from the mixture of **27** and **28** according to the procedure described earlier (82%).[4,5] A mixture of **51** and **52** in a ratio 5:1, respectively, was obtained from the mixture of **33** and **34**: IR (film) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ **51** 1.81−1.98 (m, 2H), 2.65 (ddd, 1H, J = 0.9, 7.5, 11.7 Hz), 2.23 (dd, 1H, J = 0.9, 16.4 Hz), 3.27 (ddd, 1H, J = 0.9, 2.9, 16.4 Hz), 3.58 (m, 2H), 3.98 (dd, 1H, J = 6.0, 11.7 Hz), 4.38 (m, 1H), 4.49, 4.51 (2d, 2H, J = 11.9 Hz), 5.29 (bd, 1H, J = 2.9 Hz); **52**: 1.94 (m, 2H), ∼2.83 (m, 1H), 3.15 (ddd, 1H, J = 0.6, 5.7, 10.6 Hz), 3.23 (ddd, 1H, J = 0.8, 2.7, 16.0 Hz), 3.42 (dd, J = 7.2, 10.6 Hz), ∼3.53 (m, 2H), 4.45 (m, 1H), 5.12 (bd, 1H, J = 2.7 Hz); MS (HR, EI) *m*/*z* (M^+) calcd 247.12084, obsd 247.120513.

(2*R*,6*S*)- and (2*R*,6*R*)-2-Methyl-1-oxacephams (53 and 54). A mixture of compounds **53** and **54** in proportion 1:3, respectively, was obtained from the mixture of **39** and **40** according to the procedure described earlier (72%):[4,5] IR (film) 1767 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **53** 1.26 (d, 3H, J = 6.3 Hz), 1.49−1.52 (m, 2H), 2.83 (dd, 1H, J = 0.6, 14.8 Hz), 2.97 (m, 1H), ∼3.14 (m, 1H), 3.68 (m, 1H), 3.88 (ddd, 1H, J = 1.6, 5.6, 13.5 Hz), 4.94 (d, 1H, J = 3.2 Hz); signals due to **54** 1.26 (d, 3H, J = 6.8 Hz), 1.43 (m, 1H), 2.01 (m, 1H), 2.80 (dd, 1H, J = 0.6, 14.8 Hz), 3.14 (ddd, 1H, J = 1.8, 3.3, 14.8 Hz), 3.19 (m, 1H), 3.76 (ddd, 1H, J = 3.3, 6.7, 13.5 Hz), 4.27 (m, 1H), 5.14 (dd, 1H, J = 0.6, 3.3 Hz). MS (EI, HR) *m*/*z* (M^+) calcd 141.078979, obsd 141.077352. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.57; H, 7.80; N, 9.93. Found: C, 59.32; H, 7.68; N, 9.42.

(2*S*,5*S*)- and (2*S*,5*R*)-Methylclavams (55 and 56). A mixture of compounds (**55** and **56**) in proportion 7:1, respectively, was obtained from the mixture of **47** and **48** according to the procedure described earlier (89%):[4,5] IR (film) 1784 cm^{-1}; ^1H NMR ($CDCl_3$) δ signals due to **55** 1.30 (d, 3H, J = 6.1 Hz), 2.53 (ddd, 1H, J = 0.9, 7.5, 11.6 Hz), 2.83 (dd, 1H, J = 1.0, 16.4 Hz), 3.28 (ddd, 1H, J = 0.9, 2.9, 16.4 Hz), 3.96 (ddd, 1H, J = 0.3, 5.9, 11.5 Hz), 4.36 (m, 1H), 5.33 (dd, 1H, J = 0.4, 2.9 Hz); signals due to **56** 1.36 (d, 3H, J = 6.2 Hz), 2.86 (dd, 1H, J = 0.8, 16.0 Hz), 3.16 (ddd, 1H, J = 0.9, 6.5, 10.5 Hz), 3.24 (ddd, 1H, J = 0.8, 2.7, 16.0 Hz), 3.29 (dd, 1H, J = 6.9, 10.5 Hz), 4.41 (m, 1H), 5.13 (d, 1H, J = 2.7 Hz); MS (HR, EI) *m*/*z* (M^+) calcd 127.06333, obsd 127.063362.

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