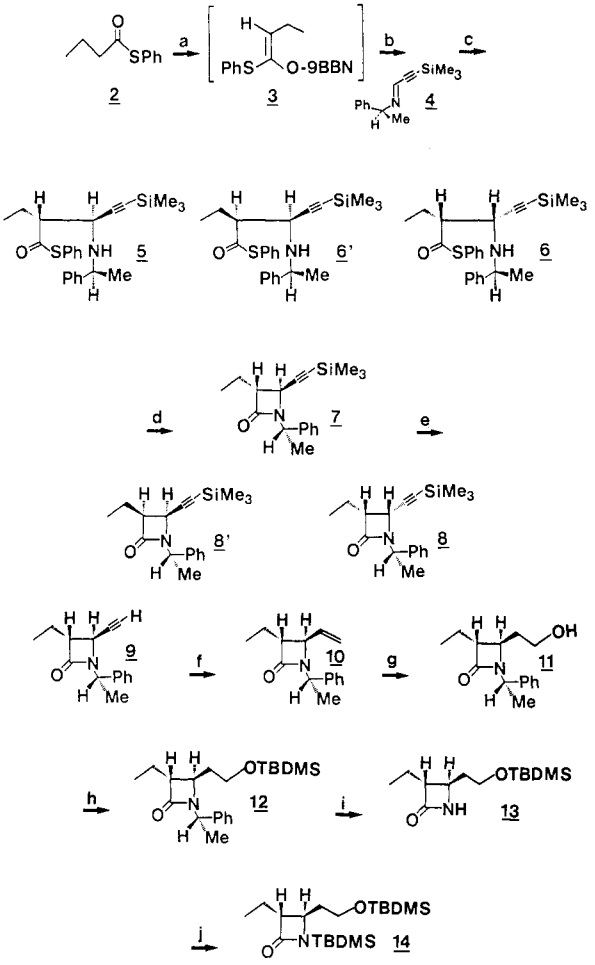
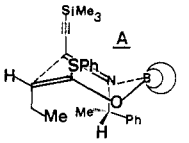
Scheme I[a]



[a] Reagents: (a) 9-BBNOTf (1.2 equiv), *i*-Pr_2EtN (1.2 equiv), CH_2Cl_2, −78 → 0 °C (1 h); (b) −40 → 25 °C (20 h), quench at −78 °C with pH 7.0 phosphate buffer; (c) concentrated HCl, ether–MeOH (2:1), 0 → 25 °C (5 h); (d) *t*-BuMgCl (2 equiv), ether, −78 → 0 °C (3 h); (e) Bu_4NF (1.5 equiv), THF, 0 °C, 0.5 h; (f) Lindlar catalyst, petroleum ether-toluene (2:1), 1 atm of H_2 pressure, 25 °C, 5 h; (g) Sia_2BH (2.5 equiv), THF, 0 °C, 2 h, and then 30% H_2O_2, 6 N NaOH, 0 → 25 °C; (h) TBDMSCl (3 equiv), Et_3N (3 equiv), DMF, 0 °C, 0.5 h; (i) Na, liquid NH_3, −78 °C, 1 h, quench with aqueous NH_4Cl; (j) TBDMSCl (3 equiv), NEt_3 (3 equiv), DMF, 0 °C, 0.5 h.

400-MHz NMR spectrum of the trans-β-lactam **7** revealed that **7** is at least 95% diastereomerically pure,[10] while the diastereomeric ratio of the cis-β-lactams is ca. 1.3:1. The trans-β-lactam **7** was then converted to **9** by treatment with tetrabutylammonium fluoride in THF (100%), followed by semihydrogenation with Lindlar catalyst (1 atm of H_2 pressure) in petroleum ether–toluene (2:1) to give **10** in quantitative yield. Exposure of **10** to disiamylborane in THF (2.5 equiv, 0 °C, 2 h) followed by oxidative workup (6 N NaOH, 30% H_2O_2) provided the hydroxy-β-lactam **11** in 91% yield. After protection of **11** as *tert*-butyldimethylsilyl ether (92%),[11] the β-lactam **12** was then treated with sodium in liquid ammonia (−78 °C, 1 h), to give **13** in 83% yield. Finally, the β-lactam **13** was converted to the disilyl β-lactam **14** in 93% yield, $[\alpha]^{25}_D$ −37.73° (*c* 2.25, $CHCl_3$) [lit.[5e] $[\alpha]^{25}_D$ −39.59° (*c* 2.92, $CHCl_3$)]. Since **14** has previously been transformed into (+)-PS-5 (**1**),[5b,d,e] this constitutes a highly efficient asymmetric synthesis of (+)-PS-5 (**1**) starting with *S*-phenyl butanethioate.

Extremely high asymmetric induction in the present condensation reaction appears to be caused by the two factors mentioned below. One is that as already pointed out by Yamamoto,[12] the asymmetric α-methylbenzyl moiety goes to the axial position in the cylic transition state, and the other is that the ethyl moiety also occupies the axial position in the cyclic transition state.[1] Owing to these factors, the transition state A appears to be the most preferable, providing the β-amino acid derivative **5** in a highly stereoselective manner.

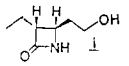


In conclusion, we wish to emphasize that the present synthesis involves the anti-selective boron enolate–imine condensation reaction with extremely high asymmetric induction as a key step.[13]

Supplementary Material Available: Experimental procedures for compounds **5**–**14** (5 pages). Ordering information is given on any current masthead page.

(10) Recently we have found that the diethylaluminum enolate of *S*-*tert*-butyl butanethioate condenses with imines in an anti-selective manner. Application of this condensation reaction to the asymmetric synthesis of (+)-PS-5 gave the unsatisfactory result in terms of asymmetric induction.

(11) The hydroxyl group was protected temporally, because the β-lactam **i** is higher water soluble.



(12) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031.

(13) After completion of this manuscript, a highly efficient asymmetric synthesis of *cis*-carbapenem antibiotics has appeared. See: Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 293.

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The Pyranoside Ring as a Nucleophile in Aldol Condensations[1]

Summary: The enolate derived from a 2-deoxy-3-keto-hexopyranoside undergoes aldol condensations in high yields. With respect to the newly formed bond, the orientation at C2 is always axial, indicating that the pyranoside moiety exerts excellent stereoselectivity at that center. Although the enolate appears to induce little facial selectivity in the aldehyde partner, α-substituents in the latter have a profound effect, the product being formed according to the Felkin–Anh model. Thus, the acetonides of *R* (D) and *S* (L) glyceraldehydes react to give syn and anti products, respectively, with complete stereoselectivity in each case.

(1) This work is supported by grants from the NSF (CHE 8304283) and NIH (GM 34350).

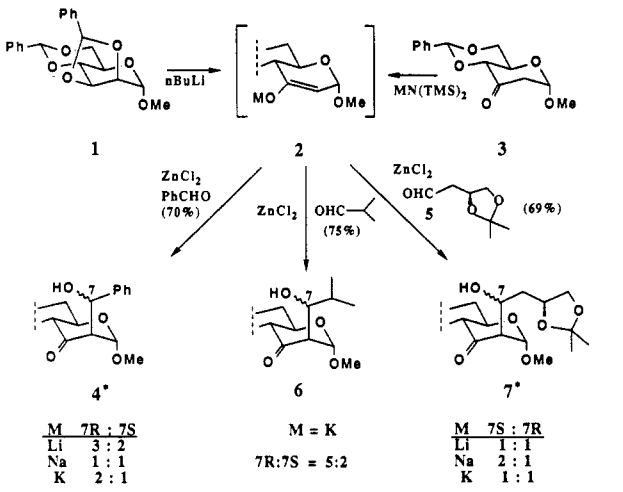
0022-3263/87/1952-3489$01.50/0

Sir: The merits of the sugar nucleus for highly stereoselective "on-template" transformations are now well chronicled.[2] However, close inspection will show that in virtually all cases, the pyranoside ring is seldom featured as a nucleophilic entity.[3] This circumstance is undoubtedly due to the fact that such a nucleophilic center would invariably carry an adjacent oxygen, which, theoretically, would be prone to β-elimination. As a result of this looming specter, the options for the use of *pyranosidic core* in convergent syntheses have been curtailed to those requiring electrophilic participation.[5] In this manuscript, we report that the 3-ketopyranose **3** can be used as the *nucleophilic* partner in aldol condensations without β-elimination of the glycosidic methoxyl and that the condensations can be totally stereoselective, thereby conforming to the expectations based on other "on-template" reactions.

Our substrate was the ketone **3**, obtained from **1** in 91% yield by fragmentation.[8,9] The intermediacy of the enolate ion **2** in the reaction indicated that the glycosidic methoxyl is surprisingly resistant to β-elimination.[10] Benzaldehyde was chosen for initial probing, but sodium, potassium, or lithium enolates gave no evidence of condensation products; however, zinc enolates, formed by metal exchange at −78 °C,[13] gave a mixture of axially oriented products, **4** (Scheme I). Similarly, isobutyraldehyde and the optically active 2-deoxytetrose **5**[14] gave mixtures **6** and **7**, respectively.

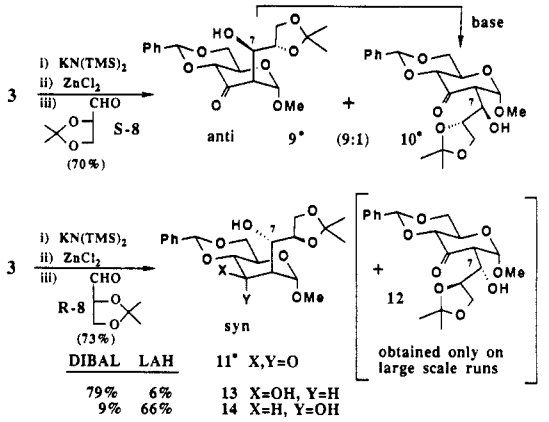
The foregoing results showed that stereoselectivity was excellent at the "on-template" (C2) site but poor at the pendant (C7) position. This implied that the enolate did not induce any facial selectivity in the attack upon the aldehyde. In the expectation that selectivity could be improved by moving the asymmetric center closer to the aldehyde, the L-glyceraldehyde derivative (*S*)-**8** was next examined (Scheme II). Two products were obtained in 70% yield, as a 9:1 mixture of isomers. Fortunately, the major isomer crystallized and X-ray analysis[15] indicated that the structure was **9** ($J_{1,2}$ = 0 Hz). In subsequent studies, it was found that **9** was isomerized to the minor product, which was therefore assigned as **10** ($J_{1,2}$ = 4.7 Hz). It seems most probable that **10** was a secondary product obtained by in situ isomerization of **9**.

Scheme I[a]



[a] Asterisk denotes that this compound gave satisfactory melting point, elemental analysis, and ^{1}H NMR data.

Scheme II[a]



[a] Asterisk denotes that this compound gave satisfactory melting point, elemental analysis, and ^{1}H NMR data.

Condensation with the D-glyceraldehyde derivative (*R*)-**8** was next examined. A single, noncrystalline product, **11**, was obtained[16] in 73% yield after chromatography, whose C2 orientation was again assignable as axial, since H-1 (δ 5.3) was unsplit. Reduction of the carbonyl group with

(2) (a) Hanessian, S. H. *Total Synthesis of Natural Products: The 'Chiron Approach'*; Pergamon Press: New York, 1983. (b) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161.

(3) There are excellent procedures for generating carbanionic reactivity at the anomeric center of some sugar derivatives, and some have provided facile routes to *C*-glyosyl compounds.[4] However, these substrates (a) are not pyranosides and (b) are always devoid of adjacent oxygens.

(4) See, for example: Beau, J. M.; Sinay, P. *Tetrahedron Lett.* **1985**, *26*, 6185, 6189, 6193. LeSimple, P.; Beau, J. M.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1985**, 894. Godoy, J., Ley, S. V.; Lygo, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1381. Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187. Nicolaou, K. C.; Hwang, C. K.; Duggan, M. E. *J. Chem. Soc., Chem. Commun.* **1986**, 925. Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926.

(5) A distinction must be drawn between those cases where a nucleophilic partner has been *derived* from a sugar[6] or where the nucleophilic center is *pendant* to the sugar ring.[7]

(6) See, for example: (a) Hanessian, S.; Pougny, J.-R.; Boessenkool, I. K. *J. Am. Chem. Soc.* **1982**, *104*, 6164. (b) Hanessian, S.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978**, *56*, 1843. (c) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224. (d) Tatsuta, K.; Tanaka, A.; Fujimoto, K.; Kinoshia, M.; Umezawa, S. *J. Am. Chem. Soc.* **1977**, *99*, 5826.

(7) See, for example: (a) Nakata, M.; Takao, H.; Ikeyama, Y.; Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1749.

(8) Klemer, A.; Rodemeyer, G. *Chem. Ber.* **1974**, *107*, 2612.

(9) Gelas, J. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 71.

(10) It has been shown that the enolate **2**, prepared in situ[11] or regenerated from **3**,[12] can be acylated or mono- and dialkylated at C2 with complete stereocontrol.

(11) Chapleur, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 141.

(12) (a) Tsang, R.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 60. (b) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116.

(13) A typical procedure was as follows: To a cooled (−40 °C) solution of ketone **3** (1.32 g, 5 mmol) in dry THF (15 mL) was added sodium hexamethyldisilazide (6.5 mmol) rapidly. The pale yellow solution was then stirred for 30 min at −40 °C and then cooled to −78 °C. Anhydrous zinc chloride (6.5 mL of 1 M solution in diethyl ether, 6.5 mmol) was added quickly, and the resultant clear solution was stirred for 15 min. Neat benzaldehyde (0.689 g, 6.5 mmol) was then added in one portion and the reaction mixture was allowed to stir at −78 °C for 30 min and then allowed to slowly warm to −40 °C. After the reaction was complete (90–120 min), it was quenched (at −40 °C) by the rapid addition of saturated aqueous ammonium chloride solution (~15 mL). The reaction mixture was diluted with ethyl acetate (20 mL), the two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo to yield a colorless solid. Flash column chromatography (1:1 petroleum ether/ethyl acetate) gave a colorless crystalline solid (1.30 g, 70%).

(14) Hanessian, S.; Ugolini, A.; Dube, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146.

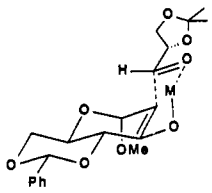
(15) Details of the X-ray analyses are given in the supplementary material.

(16) However, when the reaction was done on a larger scale (>5 g of **3**), a small amount (3–5%) of a second aldol product was obtained whose structure is assigned as **12** by comparison with **10**.

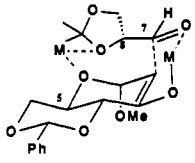
DIBAL (vide infra) gave a crystalline diol whose structure was assigned as **13** by X-ray analysis.[15]

It is of interest to examine the stereoselectivity of the reaction with respect to the two stereocenters that are being created in the aldol condensations in Scheme II. Addition from the β-face of enolate **2** to give axial adduct(s) is in keeping with the various *nucleophilic* additions to trigonal centers at C2.[17]

With respect to the other newly created center, C7, the Zimmerman–Traxler model[18] **15** correctly predicts[19-21]

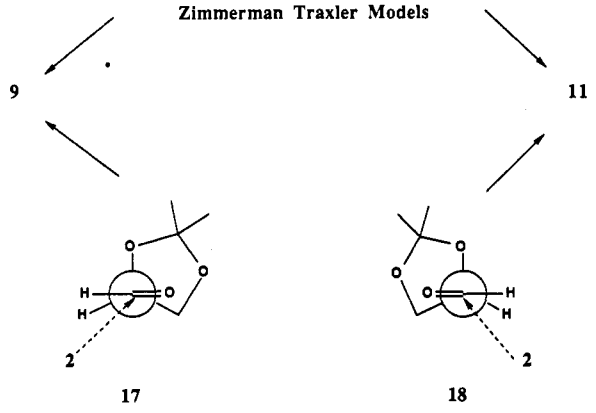


15



16

Zimmerman Traxler Models



17 **18**

Felkin-Anh Models

formation of the anti product **9** in agreement with aldol condensations involving enolates of cyclohexanones.[22] *In light of these considerations, the syn course of addition observed in 11 is an unexpected result.*[23] Thus, the corresponding transition state **16** seems highly unfavorable, since the bulky dioxolane residue is axially oriented on the six-membered chelate ring. It is tempting to note that a secondary chelation can be envisioned between O5 and O8, as indicated in **16**. Whether or not this would be enough to account for the unexpected stereochemical course remains to be seen.

As an alternative to the above, it should be noted that the Felkin–Anh models,[24,25] **17** and **18**, account for the formation of both **9** and **11**, in keeping with the preference normally observed for these aldehydes.[26]

An advantage of the homochiral primary aldol products **9** → **12** *is that, in all cases, the greater portion of the pyranosidic residue, particularly the valuable anomeric center, remains intact and available for further chemical manipulations.* The C3 carbonyl is a particularly valuable asset, as our work involving the spiro-Claisen rearrangement has shown.[27] With regard to its reduction, the equatorial or axial C3-OH, **13** and **14**, respectively, can be obtained as the overwhelming product, depending on the hydride reagent used. With lithium aluminum hydride, the result can be rationalized by postulating that the reagent chelates to the C7-OH so that the hydride ion is delivered exclusively from the β-face.

The formation of **9** → **12** indicates that the *pyranosidic core* can be a remarkably stereoselective nucleophile, complementing its traditional role as an electrophile. The basis for anti and syn selectivity (**9** vs. **11**) is intriguing and will be clarified by experiments that are currently underway.

Supplementary Material Available: Structures and tables listing details of the X-ray analyses of **8** and **12** (23 pages). Ordering information is given on any current masthead page.

(17) Several examples of these are given in ref 2a and 2b.
(18) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(19) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.
(20) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 111.
(21) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(22) See ref 18 and 19 at pages 25 and 150, respectively.
(23) It is interesting to note that Masamune's concept of "matched and mismatched" pairs[21] is not being observed here. However, it should be noted that the concept was not tested with *E* enolates, such as **2**. Furthermore, the "secondary" chelation postulated in **16** would obviously be a perturbing factor.
(24) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Anh, N. T. *Top. Curr.* Chem. **1980**, *88*, 145.
(25) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.
(26) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.
(27) Tulshian, D. B.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 2347. Fraser-Reid, B.; Tulshian, D. B.; Tsang, R.; Lowe, D.; Box, V. G. S. *Tetrahedron Lett.* **1984**, *25*, 4579.

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A Short, Efficient Synthesis of Khellinone

Summary: Thermal ring expansion of a furyl-substituted cyclobutenone has been applied to the synthesis of khellinone, a precursor to the antiatherosclerotic furochromone khellin.

Sir: The naturally occurring furochromones isolated from the fruits and seeds of *Amni visnaga L.* have long been known to possess desirable physiological activity.[1] Khellin (**4**) was found to be the most potent of the active constituents, and exhaustive investigations of its clinical and pharmacological properties have been carried out. Particular interest in khellin and its furochromone analogues was renewed by recent findings of their desirable lipid-altering activity, thus making them potential antiatherosclerotic agents.[2,3] As a result, khellin has become a popular synthetic target, and remains as such as the objective of the work described here.[4]

In this paper we wish to report a six-step synthesis of khellinone (**12**) in 52% overall yield starting with diethyl squarate. This constitutes a very efficient synthesis of khellin since it has previously been shown to be directly available from khellinone in 85% yield.[4c] A key strategy

(1) The active ingredients of the khellah plant were used by the ancient Egyptians as an antispasmodic agent.
(2) For a summary of early studies on furochromones, see: Mustafa, A. *Furopyrans and Furopyrones*; Wiley-Interscience: New York, 1967; pp 102–159.
(3) Gammill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672 and references therein.
(4) For recent khellin syntheses, see: (a) Gammill, R. B.; Hyde, B. R. *J. Org. Chem.* **1983**, *48*, 3863. (b) Gammill, R. B. *Tetrahedron Lett.* **1985**, *26*, 1385. (c) Yamashita, A. *J. Am. Chem. Soc.* **1985**, *107*, 5823.

0022-3263/87/1952-3491$01.50/0