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TRIPLE ASYMMETRIC SYNTHESIS FOR FRAGMENT ASSEMBLY: VALIDITY OF APPROXIMATE MULTIPLICATIVITY OF THE THREE DIASTEREOFACIAL SELECTIVITIES

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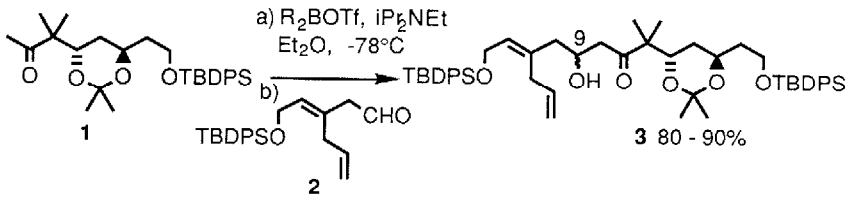
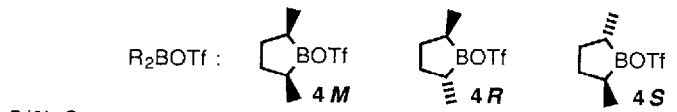
Summary: A strategy of triple asymmetric synthesis is illustrated to be effective for stereochemical control in fragment assembly, a task often encountered in convergent natural product synthesis. The stereochemical outcome of aldol reactions involving three chiral components supports a rule of approximate multiplicativity of facial selectivities intrinsic to the chiral reactants involved in each reaction.

Stereochemical control in the formation of a stereogenic center or centers is most crucial during fragment assembly for a convergent synthesis of a complex natural product. For this process, consider an aldol reaction which involves an achiral aldehyde (constituting one synthetic fragment) and an enolate derived from a chiral ketone (the other fragment). The use of a enantiomerically pure reagent to mediate the ketone enolization and subsequent aldol reaction predictably modifies the diastereofacial selectivity (D.S.) intrinsic to the corresponding enolate prepared from an achiral reagent and thereby results in enrichment of the desired diastereomeric aldol product.[1,2] Selection of a *R*- or *S*- external chiral reagent[3] provides a means of control. This strategy of external chiral reagent control is thus embodied in the precepts of double asymmetric synthesis and has recently been applied in several fragment assemblies.[1,4] Such developments suggest the possibility of attaining enhanced stereoselection upon invoking the interaction of a greater number of chiral components which react in concert. This concept has now been subjected to the experimental test and we herein record the first examples of triple asymmetric synthesis involving two chiral fragments and a chiral reagent. Two such examples (see Schemes II and III) utilize fragments made available in connection with ongoing projects aimed at the syntheses of bryostatins[5] and calyculins[6] and serve to uphold the validity of approximate multiplicativity of the diastereofacial selectivities intrinsic to the three chiral components.

The boron mediated aldol reactions involving (achiral) aldehyde **2** and (chiral) ketone **1** (Scheme I) were first examined for the purpose of comparing these reactions with those described below for triple asymmetric synthesis.[7] The reaction mediated by the achiral 2,5-*meso*-dimethylborolanyl trifluoromethanesulfonate[3] (**4*M***) established the intrinsic D.S. of ketone **1** as *ca.* 3:1 favoring the 9*S* isomer of **3**. The use of chiral (2*R*,5*R*)-dimethylborolanyltriflate (**4*R***) a reagent predicted to be matched with **1**, increased the selectivity to an 8:1 preference.[8] In contrast, (2*S*,5*S*)-dimethylborolanyl triflate (**4*S***) mediated a 1:2 preference for formation of the 9*R* stereoisomer thereby constituting a mismatched process.

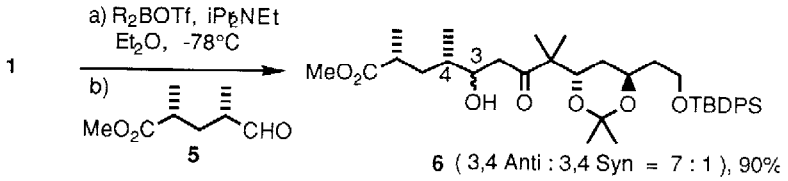
Scheme I





C(9) Stereoselectivity, (*S* : *R*) 3:1 8:1 1:2

Scheme II

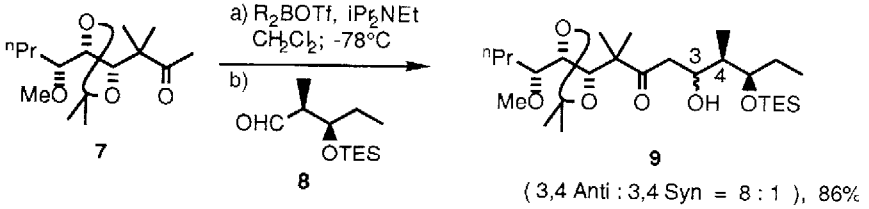


Triple Asymmetric Aldol Results

1 $\xrightarrow[\mathbf{5}]{\mathbf{4\,R}}$ **6** (3,4 Anti : 3,4 Syn = 25 : 1), 94%

1 $\xrightarrow[\mathbf{5}]{\mathbf{4\,S}}$ **6** (3,4 Anti : 3,4 Syn = 1 : 1), 92%

Scheme III



Triple Asymmetric Aldol Results

7 $\xrightarrow[\mathbf{8}]{\mathbf{4\,R}}$ **9** (3,4 Anti : 3,4 Syn = 19 : 1), 84%

$\xrightarrow[\mathbf{8}]{\mathbf{4\,S}}$ **9** (3,4 Anti : 3,4 Syn = 2 : 1), 81%

Example 1 of Triple Asymmetric Synthesis. Having secured the D.S. of ketone **1** , we chose the well studied (-)-aldehyde **5**[9] of known D.S. (*ca.* 2:1, 3,4-anti selective) to examine triple asymmetric synthesis (Scheme II). As expected for this pair (predicted at *ca.* 3×2), the double asymmetric aldol reaction with the achiral Et_2BOTf provided the aldol products **6** with a 7:1 anti/syn selection. Matched with both **1** and **5** is the chiral reagent **4*R***, and its utilization in the triple asymmetric aldol reaction enhanced the above selection to 25:1, thus exemplifying the stereoselection achieved in a fully matched system.[10] The matched-mismatched reaction using **4*S***, which led to a 1:1 formation of the diastereomers (*ca.* 3×2/3), demonstrates how selection of reagent chirality may be utilized to enhance formation of either diastereomer.[11]

Example 2. As depicted in Scheme III, a reaction between chiral ketone **7**[12] with (+)-aldehyde **8**[13] mediated by Et_2BOTf afforded the aldol products **9** with an 8:1 anti/syn selection. The use of triple asymmetric synthesis in this instance through mediation with the **4*R*** reagent enhanced the selectivity to afford a 19:1 anti/syn diastereomeric ratio. Utilization of the **4*S*** reagent enabled significant formation of the 3,4-syn diastereomer with an anti/syn ratio of 2:1.[14,15]

The above two examples validate an approximate multiplicativity rule even for triple asymmetric synthesis. High levels of stereocontrol are readily attained for systems consisting of three matched components. The results also indicate that reagents with a larger D.S. than those described above will override any opposing substrate preference in mismatched systems, providing full stereochemical control, simply through the selection of a proper reagent. Triple asymmetric synthesis will prove to be a powerful strategy for fragment assembly with controlled creation of correct stereochemistry.

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References and Footnotes

1. A subtle but important distinction should be noted between fragment assembly and stereo-selective addition of acetate and propionate equivalents to a chiral aldehyde via the aldol reaction. See: Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* **1989**, *54*, 2817.

2. For reviews of double asymmetric synthesis, see: (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1. (b) Sharpless, K. B. *Chimica Scripta* **1985**, *25*, 71. (c) Masamune, S.; in *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W.; Sharpless, K. B., Ed.; VCH Verlagsgesellschaft mbH, Weinheim, **1987**: pp. 49-71.

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4. (a) Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587. (b) Paterson, I.; Lister, M. A.; *Tetrahedron Lett.* **1988**, *29*, 585. (d) Paterson, I.; McClure, C. K. *Tetrahedron* **1987**, 1229.

5. Potent antineoplastic agents, first isolated: Pettit, G. R.; Day, J. F.; Hartwell, J. L.; Wood, H. B. *Nature* (London) **1970**, *227*, 962. See also (a) Pettit, G. R.; Herald, C. L.; Doubec, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846. (b) Pettit, G. R.; Leet, J. E.; Herald, C. L.; Kamano, Y.; Boettner, F. E.; Baczyncky, L.; Nieman, R. A. *J. Org. Chem.* **1987**, *52*, 2854.

6. Antitumor sponge metabolites; see: (a) Kato, Y.; Fusetani, N.; Matsunga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780. (b) Kato, Y.; Fusetani, N.; Matsunga, S.; Hashimoto, K.; Fujita, S.; Furuya, T.; Kaseki, K. *Abs. for 28th Natural Prod. Sym., Japan* **1986**, 168.

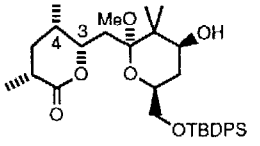
7. The preparation and use of aldehyde **2** was described in an earlier approach to 4 the bryostatins (see Ref. 1). The synthesis of ketone **1** will be reported at a later date as part of a full account on our bryostatin studies.

8. *ca.* 3x3: The D.S. of the borolanyl reagent has been measured at 3-4:1 from reactions of t-butyl methyl ketone with various achiral aldehydes: Kim, B.-M; PhD Thesis, Massachusetts Institute of Technology 1987, pp. 114-131.

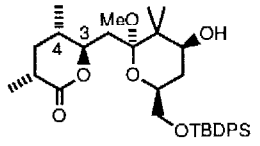
9. Short, R. P.; Masamune, S. *Tetrahedron Lett.* **1987**, *28*, 2841.

10. The aldol reaction of ketone **1** with the (+)-aldehyde **5** as mediated by Et_2BOTf resulted in formation of a 1:1 mixture of diastereomeric aldol adducts, and this pair constituted a mis-matched pair.

11. The **6**-syn and **6**-anti mixtures were quantitatively converted to the pyranyl lactones **i** and **ii**, respectively, and measurement of the $J_{3,4}$ value in **i** and **ii** confirmed the stereo-selection in the aldol process.



i ($J_{3,4}$ = 3 Hz, ax.-eq.)

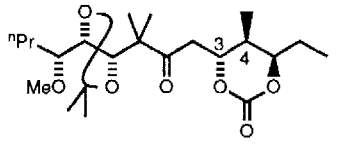


ii ($J_{3,4}$ = 10 Hz, ax.-ax.)

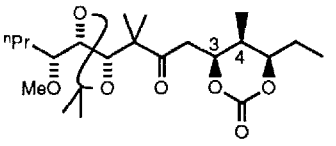
12. The synthesis of ketone **7** will appear at a later date in relation to studies on the total synthesis of calyculin A.

13. (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *Ibid.* **1981**, *103*, 1568.

14. The **9**-anti and **9**-syn products were converted to the corresponding cyclic carbonates **iii** and **iv**, respectively. Assignment of absolute configuration was accomplished by comparison of the $J_{3,4}$ value in **iii** and **iv**.



III ($J_{3,4}$ = 4 Hz, eq.-eq.)



Iv ($J_{3,4}$ = 2 Hz, ax.-eq.)

15. Experimental and characterization data for compound **1**, **3**, **6**-**9**, and **i**-**iv** are available from S.M. upon request.

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