Chiral Auxiliary-Mediated Asymmetric Induction in a Thermal Inverse Electron Demand Hetero-Diels–Alder Reaction. Enantioselective Synthesis of the Taxol A-Ring Side Chain

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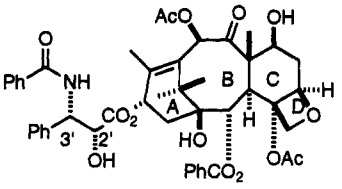
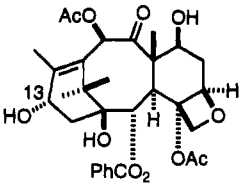
Received August 3, 1993•

Summary: Chiral auxiliary-modified ketene acetal **5g** and *N*-benzoylbenzaldimine (**4**) engage in an endo and π-facially selective thermal inverse electron demand hetero-Diels–Alder reaction that is the key step in a synthesis of enantiomerically pure taxol A-ring side-chain methyl ester **9**.

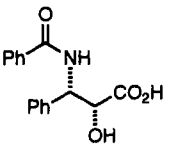
The evolution of taxol[1] into a highly significant antitumor drug[2] and its current scarcity[3] have focused attention on the synthesis[4] and attachment[4e,5] to naturally derived taxanes like baccatin III[6] of the taxol A-ring side chain (**1**), without which (i.e., as in baccatin III) important biological activity is not expressed.[1] In a recent report on partial syntheses of selected taxol analogs,[7] we speculated that dihydroketooxazines like **2** might be effective acylating agents toward the hindered and poorly reactive baccatin III C-13 hydroxyl, thereby leading to efficient partial syntheses of taxol and analogs. That concept has been demonstrated by Holton.[4e] Insofar as dihydrooxazines like **3** can arise from inverse electron demand hetero-Diels–Alder reactions,[8] they suggested, as well, the new assembly



TAXOL



BACCATIN III



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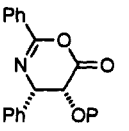

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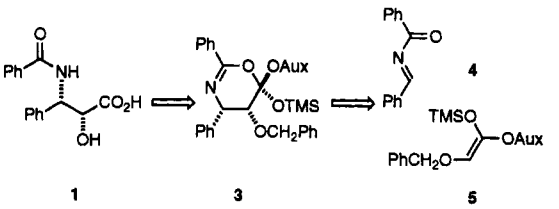
of the taxol A-ring side chain depicted below. Herein we report that the taxol A-ring side chain may be constructed enantioselectively through a thermal, chiral auxiliary-mediated variant of this cycloaddition.[9]



1 **3** **5**

The enantioselective construction of the taxol A-ring side chain through intermediates of type **3** requires (1) that the cycloaddition delivering them proceed through an endo transition structure[10] and (2) that the chiral auxiliary causes the ketene acetal to experience an acceptable degree of π-facial discrimination. The literature[11] provided little guidance regarding the transition

• Abstract published in *Advance ACS Abstracts,* October 1, 1993.

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(10) In point of fact, to achieve the synthesis goal at hand it is only necessary that the $PhCH_2O$ group in either geometrical isomer of ketene acetals **5** be disposed endo in the cycloaddition with **4**.

(11) For cycloadditions involving **4**. However, Boger has shown that certain 1-aza dienes engage in endo-selective thermal inverse electron demand hetero-Diels–Alder cycloadditions with electron-rich (oxygenated) alkenes. See: Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713.

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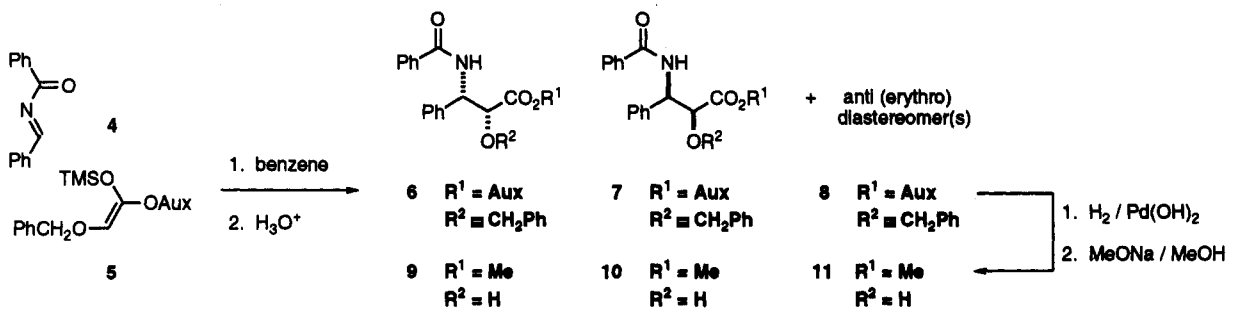
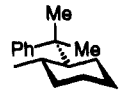
Scheme I



entry	Aux	ketene acetal	cycloaddition temperature	yield (6+7+8; %)	ratio 9 : 10 : 11
1	Me	5a	ambient	50	50 : 50[a]
2	C_6H_{11}	5b	ambient	47	79 : 21[a]
3	 (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheyl	5c	0 °C ambient reflux	52 64 55	25 : 75 : 0 25 : 75 : 0 30 : 70 : 0
4	 (1*R*,2*S*)-(−)-*trans*-2-phenyl-1-cyclohexyl	5d	reflux	47	70 : 18 : 12
5	 (1*R*,2*S*,5*R*)-(−)-menthyl	5e	ambient	55	20 : 75 : 5
6	 (1*R*,2*S*,5*R*)-(−)-8-phenylmenthyl	5f	0 °C ambient reflux	64 70 49	0 : 91 : 9 0 : 90 : 10 5 : 82 : 13
7	 (1*S*,2*R*)-(+)-*trans*-2-(1-methyl-1-phenylethyl)-1-cyclohexyl	5g	ambient	75	93 : 0 : 7

[a]Racemic syn (threo) **6/7** : racemic anti (erythro) **8**.

structure to be expected. However, the interaction of *Z*[12] ketene acetal **5a** with *N*-benzoylbenzaldimine (**4**)[13] followed by aqueous acid workup[14] furnished a 50:50 mixture of racemic syn methyl ester **6a/7a** and racemic anti methyl ester **8a**, respectively, whereas a similar experiment with *Z* ketene cyclohexyl acetal **5b** led to a 79:21 mixture of racemic **6b/7b** and racemic **8b**, respectively (Scheme I). The syn/anti diastereomer ratios were evaluated by GC–MS; confirmation of the structural assignments was made by comparison to authentic materials[4] through ^{1}H NMR spectroscopy. These observations indicate that no intrinsic electronic bias is operative toward either the endo or exo cycloaddition transition structures, but the steric influence of the cyclohexyl group can impart a modest preference for the endo transition structure responsible for the formation of **3** and, thus, the syn taxol A-ring side-chain diastereomer to which it leads.[15]

Since most chiral auxiliaries would be expected to exert a steric effect greater than cyclohexyl, we turned next to an examination of chiral auxiliary-mediated ketene acetal π-facial discrimination. *Z* Ketene acetals **5c–g** were prepared from the corresponding (benzyloxy)acetate esters by treatment with LHMDS and TMSCl in THF in the case of **5c–e**, whereas **5f,g** were prepared from the same ester-silylating agent–solvent combination and lithium cyclohexylisopropylamide. *N*-Benzoylbenzaldimine (**4**) and the chiral auxiliary-modified ketene acetals were then combined[14] to give, after aqueous acid workup of the cycloaddition reaction mixtures, syn and anti diastereomers **6–8** (combined yield indicated). For the removal of the chiral auxiliaries and the determination of the levels of asymmetric induction, the mixtures of **6–8** were sequentially debenzylated (68%-quantitative) and transesterified (56–82%) to afford taxol A-ring side chain methyl

(12) For chelation control of *Z* enolate formation from α-alkoxy esters, see, for example: Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Märki, H.-P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161.

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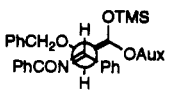
(14) Cycloaddition–hydrolysis procedure (Scheme I): 2 mmol of ketene acetal **5** (100% *Z*) and 2.4 mmol of *N*-benzoylbenzaldimine **4** in 8 mL of benzene were stirred at the indicated temperature for 2–14 h. Workup with dilute aqueous HCl gave **6–8**.

(15) We cannot unequivocally eliminate open transition structure *i* below. However, we regard the dependence of the syn–anti stereoselectivity on the steric requirement of the Aux substituent as inconsistent with this transition structure.

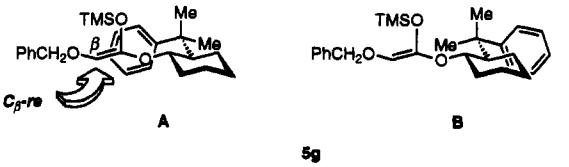


I (syn)

ester enantiomers **9** and **10** and the analogous anti methyl ester diastereomer **11**. The **9**:**10** enantiomer ratios were evaluated by ^{1}H NMR spectroscopy using Eu(hfc)$_3$. The natural 2′*R*,3′*S* enantiomer of the taxol A-ring side-chain methyl ester (**9**) produced in entry 7 in Scheme I exhibited $[\alpha]^{22}_D = -49.7°$ (c = 0.458; MeOH) [lit.[1] $[\alpha]^{23}_D = -49.6°$ (MeOH)].

As expected, the chiral auxiliaries employed in Scheme I led to better levels of endo–exo discrimination than did cyclohexyl. However, the best in this regard—(−)-isopinocampheyl[16] (**5c**)—enforced disappointing π-facial discrimination, as did (−)-*trans*-2-phenyl-1-cyclohexyl[17,18] (**5d**) and (−)-menthyl[17] (**5e**). (−)-8-Phenylmenthyl[17,19] (**5f**) led to the taxol A-ring side-chain methyl ester in excellent enantiomeric purity, but, as with the remaining two terpene-related auxiliaries, in the unnatural 2′*S*,3′*R* enantiomeric form. Notably, the (−)-*trans*-2-phenyl-1-cyclohexyl auxiliary, related in its absolute stereochemistry to (−)-8-phenylmenthyl, led mainly to natural 2′*R*,3′*S* taxol A-ring side-chain methyl ester enantiomer **9**. Examples of the reversal of the sense of asymmetric induction caused by *trans*-2-phenyl-1-cyclohexyl versus the spatially related enantiomer of 8-phenylmenthyl have been reported by Whitesell.[20] Comins[21] recently developed convenient preparations of both enantiomeric forms of the 8-phenylmenthyl surrogate—*trans*-2-(1-methyl-1-phenylethyl)-1-cyclohexyl.[22] The (1*S*,2*R*)-(+)-*trans*-2-(1-methyl-1-phenylethyl)-1-cyclohexyl auxiliary related to the enantiomeric form of (1*R*,2*S*,5*R*)-(−)-8-phenylmenthyl was incorporated into ketene acetal **5g** and, as expected from the experience with **5f**, delivered **9** through a cycloaddition characterized by good endo and excellent π-facial selectivity.

The transition structures involved in the present cycloadditions are not subject to organization by Lewis acid ligation and might be expected to reflect the ground-state conformational biases of the ketene acetals. A model for ground-state **5g** that accounts for its π-facial selectivity and is supported by a conformational search for the related dimethoxy structure[23] (MeO instead of TMSO and $PhCH_2O$) is indicated below (**A**). This conformation lies



5g

approximately 1.8 kcal-mol^{-1} lower in energy than the next type encountered (**B**), for which reduced π-facial discrimination would be expected. The origin of the π-facial selectivities observed for **5f** and **5g** aside, this report suggests that high levels of chiral auxiliary-mediated asymmetric induction might be generally attainable in thermal inverse electron demand hetero-Diels–Alder reactions.

Acknowledgment. Support through USPHS Grant No. CA 55139 awarded by the National Cancer Institute, DHHS is gratefully acknowledged. We would like to express our gratitude to Professor Daniel L. Comins, North Carolina State University, for providing the experimental details for the preparation of the enantiomerically pure alcohol that led to **5g** and to Dr. Lisa E. Chirlian for performing the molecular modeling calculations.

Supplementary Material Available: Preparative procedures and physical data for all new compounds reported herein (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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