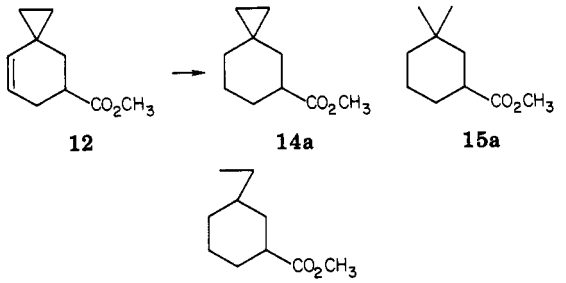
Scheme III



12 14a 15a 16a

	combined yield, %	14a	15a	16a
a, $[(C_6H_5)_3P]_3RhCl$, benzene	84	100		
b, PtO_2/AcOH	93		97	03
c, 10% Pd/C, THF, H_2O	92	16		84

less pronounced with nitroethylene (Table II).

The structure of each adduct was proven by ^1H NMR analysis.[13] Moreover, the structure of the adduct obtained from acrylate has been proven beyond doubt by comparison of the NMR and IR spectra of the derived acid with the spectra of an authentic sample prepared by a totally different route by Yates et al.[14]

We have found that the vinylcyclopropane system present in the spirooctene derivatives can serve as precursor of spirooctanes, of *gem*-dimethylcyclohexanes, or of ethylcyclohexanes. Our results on the acrylate adduct **12a** are herein reported. Thus we found that the carbon–carbon double bond in **12a** can be selectively (100%) reduced by hydrogen if the reaction is performed in the presence of a rhodium catalyst ($[(C_6H_5)_3P]_3RhCl$, 0.1 molar equiv, benzene, 20 °C, 10 h; **14a**, 84% yield) (Scheme III). However, the nature of the product(s) formed critically depends upon the nature of the catalyst used.[15] For example, the dimethylcyclohexane **15a** resulting from the concomittant reduction of the double bond and of the cyclopropane ring was quite exclusively formed (**15a**/**16a** = 97:3) if platinum is used (Pt, 0.3 molar equiv, CH_3CO-OH, 20 °C, 4 h, 93% yield), while the ethylcyclohexane **16a** formally formed through a 1,5-reduction was obtained (**16a**/**14a** = 84:16) if the reaction is conducted over palladium (Pd/C 10%, 20% (w/w), THF/H_2O (1:1), 20 °C, 4 h, 92% yield). Further work on more substituted dienes will be reported in due course.

Registry No. **2**, 670-54-2; **5**, 108-31-6; **8**, 41596-88-7; **9**, 84864-32-4; **10**, 80119-20-6; **11a**, 84864-33-5; **11b**, 84864-34-6; **11c**, 84864-35-7; **11d**, 84864-36-8; **11e**, 84864-37-9; **11f**, 84864-38-0; **12a**, 84864-39-1; **12b**, 84864-40-4; **12c**, 84864-41-5; **12d**, 84864-42-6; **12e**, 84864-43-7; **12f**, 84864-44-8; **12g** (isomer 1), 84864-45-9; **12g** (isomer 2), 84864-46-0; **13c**, 84864-47-1; **13d**, 84864-48-2; **14a**, 84864-49-3; **15a**, 84864-50-6; **16a**, 84864-51-7; *p*-benzoquinone, 106-51-4; dimethyl acetylenedicarboxylate, 762-42-5; dimethyl fumarate, 624-49-7; dimethyl maleate, 624-48-6; methyl acrylate, 96-33-3; 3-buten-2-one, 78-94-4; 2-propenal, 107-02-8; nitroethene, 3638-64-0; methyl methacrylate, 80-62-6; 2-methyl-2-propenal, 78-85-3; (*E*)-2-butenal, 123-73-9.

(13) NMR of the acrylate adduct **12a** (Jeol MH 100, 100 MHz, CCl_4, Me_4Si as internal standard): δ 5.49 (dt, J = 10.0, 3.5 Hz, 1 H), 4.92 (br d, J = 10 Hz, 1 H), 3.57 (s, 3 H), 2.60 (m, $\sum J$ = 28 Hz, 1 H), 2.22 (m, 2 H), 1.92 (dd, J = 12, 10 Hz, 1 H), 1.35 (dd, J = 12.0, 3 Hz, 1 H), 0.52 (s, 4 H).

(14) (a) We thank Prof. Peter Yates for providing us with the IR and NMR data of that compound.[14b] (b) Yates, P.; Fenwick, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 4618.

(15) Rylander, P. N. "Catalytic Hydrogenation in Organic Synthesis"; Academic Press: New York, 1979; Chapter 14, p 251.

F. Zutterman, A. Krief*

Facultés Universitaires Notre-Dame de la Paix
Département de Chimie
B-5000-Namur, Belgium

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Asymmetric Diels–Alder Reaction: Design of Chiral Dienophiles

Summary: An asymmetric Diels–Alder reaction between cyclopentadiene and a new chiral dienophile is described. Excellent diastereofacial selectivity can now be achieved even in the *absence* of a catalyst. The stereochemical result of this reaction has been rationalized on the basis of a rigid hydrogen-bonded cisoid conformation of the ketol-type dienophile.

Sir: The use of a chiral dienophile or enophile[1] in the Diels–Alder reaction effects (single)[2] asymmetric induction, the degree of which is expressed by the diastereofacial selectivity[3] of either chiral reactant. This asymmetric Diels–Alder chemistry, pioneered by Korolev and Mur[4] and Walborsky et al.,[5] has received renewed interest in recent years,[6] and, indeed, *with the aid of a Lewis acid catalyst*, some reactions now proceed with very high and sometimes near-perfect diastereoselection.[7] After a close review of this development, our attention has been directed to the design of chiral dienophiles in which a chiral auxiliary is attached one atom closer to the three-carbon enone unit (type I) than in those (type II) often used earlier.[6,7] The

I II

outcome brought about by this simple design change is significant, and even *in the absence of an external catalyst* (*vide supra*), a new dienophile described below attains a diastereofacial selectivity as high as >100:1. To our best knowledge, the highest ratio thus far recorded for the *uncatalyzed* reaction has been 80:20.[8]

(1) Chiral Lewis acids also effect asymmetric induction: Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.

(2) The phase "single asymmetric induction" is used when only one chiral reactant participates in a reaction. Similarly, multiple (double, triple...) asymmetric induction is defined.

(3) For the definition of this phrase, see (a) Masamune, S.; Lu, L.D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523 (footnote 16). For a detailed discussion, see (b) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47.

(4) Korolev, A.; Mur, V *Dokl. Akad. Nauk. SSSR* **1948**, *59*, 251; *Chem. Abstr.* **1948**, *42* 6776*f*.

(5) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 4778.

(6) For a recent review, see: Mori, Y. *J. Syn. Org. Chem.* (Yuki Gosei Kagaku) **1982**, *40*, 321. Also see (b) Oppolzer, W. "Diastereo- and Enantioselective Cycloaddition of the Ene Reactions in Organic Synthesis" presented at the Fourth International Conference on Organic Synthesis, Tokyo, 1982.

(7) For an enophile, see (a) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595. For a dienophile, see: (b) Oppolzer, W.; Chapuis, C.; Dao, G. M.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4781.

(8) (a) Helmchen, G.; Schmierer, R. *Angew, Chem., Int. Engl.* **1981**, *20*, 205. A claim of high asymmetric induction was made: (b) Horton, D.; Machinami, T. *J. Chem. Soc., Chem. Commun.* **1981**, 88. However, their reported specific rotation for the *R* enantiomer of the methyl ester of **8** was "$[\alpha]_D$ −10°, $CHCl_3$", which was compared with $[\alpha]^{25}_D$ −10.2° (*c* 1.8, 95% EtOH) recorded for the same ester obtained through partial resolution (estimated optical purity, 35%, see ref 11) by (c) Berson, J. A.; BenEfraim, D. A. *J. Am. Chem. Soc.* **1959**, *81*, 4083.

0022-3263/83/1948-1137$01.50/0

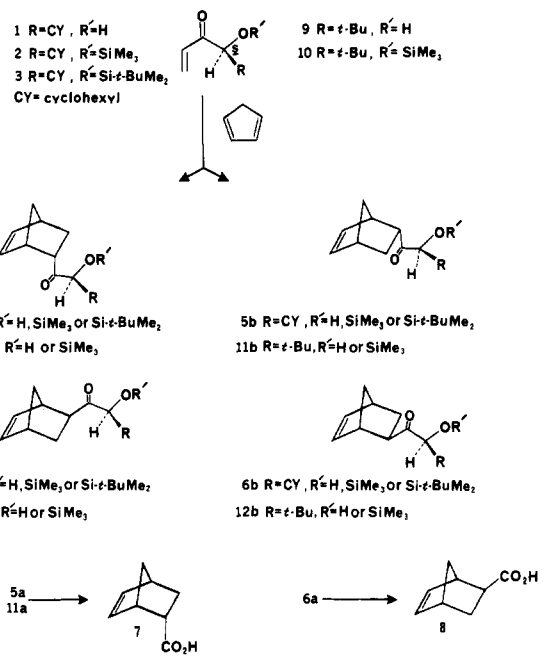
Table I. Asymmetric Diels–Alder Reactions of 1-3, 9, and 10 with Cyclopentadiene[a,b]

entry	dienophile	conditions, °C (h)	ratio of 5a:5b or 11a:11b	ratio of 6a:6b or 12a:12b	ratio of endo to exo: (5a + 5b) to (6a + 6b), (11a + 11b) to (12a + 12b)
1	1	rt[d] (2)	13:1	8:1	8/1
2	1	−20 (18)	20:1	6.5:1	9/1
3	1	−55 (170) 80% conversion	28:1	7:1	6/1
4	2	rt (12)	40:60	1:1	3/1
5	2	−20 (210) 94% conversion	36:64	1:1	3/1
6	3	rt (18)	60:40	60:40	3/1
7	3	−20 (190)	60:40	64:36	78:22
8	9	rt (1)	23:1	c	6:1
9	9	0 (10)	60:1	c	6:6
10	9	−20 (24)	>100:1	c	8:1
11	10	rt (24)	40:60	38:62	85:15

[a] Reactions that required longer than 1 day for at least 80% completion were conducted in 0.5 M toluene solution. Otherwise reactions were carried out in 0.2 M solution. [b] Diastereomeric ratios shown in columns 4 and 5 were determined by integration of several comparable sets of signals of each pair of diastereoisomers in the 250- or 270-MHz ^{1}H NMR spectra. [c] Ratios could not be determined because product 12b could not be detected by the above spectral method (detection limit, ca. 1%). [d] Room temperature.

The dienophiles 1–3 were prepared in a manner similar to that of ketone 4 (ethyl instead of vinyl in 3),[9] a reagent that possesses high diastereofacial selection in the aldol process and that has been applied successfully to our macrolide synthesis.[3b] Thus, treatment of (*S*)-hexahydromandelic acid[9] with 3.5 equiv of vinyllithium (in tetrahydrofuran, −78 °C to room temperature) yielded (70%) ketol 1, $[\alpha]^{20}_D$ +180.4° (*c* = 1.02, $CHCl_3$), which, in turn, was silylated to give enone 2, $[\alpha]^{20}_D$ −81.0° (*c* 1.83, $CHCl_3$) (with trimethylsilyl chloride and *N*,*N*-diisopropylethylamine in dichloromethane), or enone 3, $[\alpha]^{20}_D$ −65.5° (*c* 1.66, $CHCl_3$) (with *tert*-butyldimethylsilyl triflate and 2,6-di-*tert*-butylpyridine in dichloromethane).[10] The reactions of these dienophiles 1–3 with distilled cyclopentadiene (5–10 equiv) in toluene were carried out to at least 80% completion, and the absolute configurations of the newly created chiral centers in the products, endo-diastereomers **5a** and **5b** and exo diastereomers **6a** and **6b**, were established through the oxidative degradation; hydrolysis of the silyloxyl group with dilute aqueous acid, if necessary, and then sodium metaperiodate oxidation of **5a** and **6a** into the acids 7 and 8 of known configurations, respectively (Scheme I).[11]

Scheme I



The results of the above Diels–Alder reactions are summarized in Table I (entries 1–7) in which two notable features are evident. While the silylated dienophiles 2 and 3 exhibit inferior endo/exo selection (last column) as well as insignificant diastereofacial selections (**5a**/**5b** and **6a**/**6b**; entires 4–7), both selections with ketol 1 are remarkably high and nearly rival the highest ratios reported for chiral ester of type II in reaction catalyzed by a Lewis acid.[6,7b] These high selections almost certainly are attributed to the strong hydrogen bonding between the hydroxyl and ketonic functions in 1. The formation of a five-membered chelate effectively freezes the free rotation along the C(=O)—C(asym) axis, thus making the two diastereotopic faces of the enone system highly distinguishable. Support for this inference is found in an infrared spectral study on ketol 1 that shows only one hydroxyl absorption (3492 cm^{-1}) with varying concentrations (0.5–0.005 M in carbon tetrachloride). This hydrogen bonding stabilization would be tenable also in the transition state of the reaction.

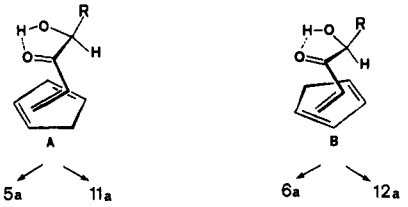
Another feature concerns the stereochemical relationship between the dienophile 1 and the favored endo and exo diastereomers (**5a** and **6a**) that have formed in the reaction. From the established absolute configurations of these compounds, we infer that, with the chelated framework of ketol 1, the Diels–Alder reaction proceeds with the enone fragment in its cisoid (synplanar) conformation in this particular instance (as opposed to the transoid conformation often postulated earlier for chiral esters of type II). Thus, the favored transition states A and B lead to the

(9) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

(10) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455. The use of 2,6-lutidine as recommended in this letter resulted in a lower yield of 3.

(11) Calculated optical rotations of 7, $[\alpha]^{20}_D$ −144.04, and 8, $[\alpha]^{20}_D$ +17.08, have been reported: Berson, J. A.; Walia, J. S.; Remanick, A.; Suzuki, S.; Reynolds-Warnhoff, P.; Willner, D. *J. Am. Chem. Soc.* **1961**, *83*, 3986. Degradation of compound **5a** provided 7, $[\alpha]^{20}_D$ −139.0 (*c* 1.38, 95% EtOH). Reduction of compound **11a** with Dibal, followed by $NaIO_4$ cleavage and Jones oxidation gave pure 7, $[\alpha]^{20}_D$ −147.14 (*c* 0.49, 95% EtOH). Similar treatment of compound **12a** gave pure 8, $[\alpha]^{20}_D$ +18.39 (*c* 0.62, 95% EtOH).

corresponding products **5a** and **6a** as shown below.



The above analysis suggests that the dienophile **9** with a *tert*-butyl substituent would exhibit even more enhanced diastereofacial selectivity than **1**. Molecular models indicate that (1) within the chelated framework the energy difference between the cisoid and transoid conformers of **9** is definitely greater than that in the case of **1** (because of the severe repulsion between vinylic hydrogens and the *tert*-butyl group of the transoid conformer of **9**), and (2) the steric interactions between the *tert*-butyl group of **9** and the approaching cyclopentadiene would be greater than that between the cyclohexyl group of **1** and the same diene. This prediction has indeed proven valid. The known (*S*)-2-hydroxy-3,3-dimethylbutyric acid, $[\alpha]^{20}_D$ +4.45° (*c* 4.0, H_2O),[12] resolved from its racemic mixture with (−)-1-phenylethylamine was converted to **9**, $[\alpha]^{20}_D$ +205.9° (*c* 2.64, $CHCl_3$), and compound (**9**) and its trimethylsilyl derivatives **10** $[\alpha]^{20}_D$ −58.8° (*c* 0.49, $CHCl_3$), were allowed to react with the diene in a manner analogous to that for **1** and **2**. As summarized in entries 8–11 in Table I, our expectations are fully realized, and at −20 °C the enone **9** attains a diastereofacial selectivity of >100:1 in the formation of the two endo diastereomers **11a** and **11b** (entry 10).[13] While there is room for further improvement in the endo/exo ratio, the design of reagents **1** and **9** has definitely demonstrated one rational approach to the asymmetric Diels–Alder reaction. Further work is underway.

Acknowledgment. We thank Professor W. Oppolzer for the written version of ref 6b and the National Institutes of Health (CA 28337) for financial support. High-resolution mass spectra were provided by the facility supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann), from the Biotechnology Resources Branch, Division of Research Resources, and infrared studies were performed with a Nicolet NIC-7199 FT-IR system purchased through an NIH grant (GM 27551).

Registry No. **1**, 85067-27-2; **2**, 85082-16-2; **3**, 85082-17-3; **9**, 85067-28-3; **10**, 85067-29-4; cyclopentadiene, 542-92-7.

Supplementary Material Available: Listing of spectral data (3 pages). Ordering information is given on any current masthead page.

(12) Tanabe, T.; Yajima, S.; Imaida, M. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2178. The reported specific rotation for this acid is $[\alpha]^{20}_C$ +4.50° (*c* 4, H_2O).

(13) The enantiomeric purity of all new compounds (except for the carboxylic acids) has been assessed by ^1H NMR spectroscopy, using $Eu(Hfbc)_3$, or by the Mosher acid chloride procedure [Dale, T. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.]

William Choy, Lawrence A. Reed, III
Satoru Masamune*
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received December 22, 1982

The Nitrile Oxide Cycloaddition (NOC) Route to a Multipurpose *C*-Nucleoside Intermediate: A New Class of *C*-Nucleosides

Summary: A new route to the important class of antibiotic and antiviral agents, the *C*-nucleosides, has been developed. The nitrile oxide generated from a protected derivative of β-D-ribofuranosylnitromethane has been shown to react with ethoxyacetylene to deliver an isoxazole *C*-nucleoside. On hydrogenolytic cleavage of the N–O bond, a β-keto ester is formed that can be reacted with a bisnucleophile to yield a new *C*-nucleoside analogue.

Sir: In further extending the application of nitrile oxide cycloaddition chemistry to other molecules of Nature, it was reasoned that the generation of nitrile oxides bearing sugar units and their fragments could well prove to be of considerable importance to synthesis design.[1] As an example of this notion, we report herein a novel and very efficient route to a new class of *C*-nucleoside products containing ribose attached to an isoxazole. Furthermore, we show in one example how such *C*-nucleosides can in turn provide access to a host of related *C*-nucleoside structures.

Our work began with the known α- and β-D-ribofuranosylnitromethane derivatives **1α** and **1β**. These products are conveniently prepared by reacting a methanol solution of D-ribose with nitromethane in the presence of potassium carbonate (Scheme I). This procedure delivered the α-isomer in ~17% yield and the β-isomer in ~62% as described by Sudoh et al.[2] Each isomer was converted to its acetonide derivative (2,2-dimethoxypropane, THF, TsOH), and the remaining hydroxyl group was protected by silylation (t-Bu(Me)$_2$SiCl, imidazole). Since some epimerization of these isomers occurs during the protection process,[3] it has proven most convenient to carry out rigorous purification of each isomer after the silylation step rather than after the initial nitromethane condensation reaction.

With the pure D-ribofuranosylnitromethane derivatives **2α** and **2β** in hand, we were now ready to test the key nitrile oxide cycloaddition reaction. Since some initial concern did exist as to whether epimerization of the β-isomer to the α-isomer (the thermodynamically favored isomer)[4] might occur during the nitrile oxide forming step (PhNCO, Et_3N), care was taken to use very pure samples of **2α** and **2β** during the initial stages of the investigation.

On reaction of **2α** or **2β** with ethoxyacetylene[5] under the Mukaiyama conditions,[6] pure **3α** and **3β** were formed in high yield. Little, if any, epimerization was found to occur with either isomer, a fact that can be attributed to rapid interception of the nitronate anion by the phenyl isocyanate to generate the transient nitrile oxide without competing β-elimination of the tetrahydrofuranyl ring

(1) For some recent examples of such applications, see: Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788. Kozikowski, A. P.; Stein, P. D. *Ibid.* **1982**, *104*, 4023. Kozikowski, A. P.; Ishida, H. *Ibid.* **1980**, *102*, 4265. Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248. Kozikowski, A. P.; Ghosh, A. K., manuscript in preparation. Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.* **1982**, *23*, 2081.

(2) Sakakibara, T.; Takamoto, T.; Matsuzaki, T.; Omi, H.; Maung, U. W.; Sudoh, R. *Carbohydr. Res.* **1981**, *95*, 291.

(3) After acetonide formation using pure **1β**, an 84:16 mixture of the protected β- and α-products was obtained. Silylation of the acetonide derivative of **1β** gave a 9:1 mixture of the β- and α-products, respectively, after 12 h. If the silylation reaction was kept at room temperature for 6 days, a 45:55 mixture of the β- and α-products resulted.

(4) Takamoto, T.; Omi, H.; Matsuzaki, T.; Sudoh, R. *Carbohydr. Res.* **1978**, *60*, 97.

(5) Jones, E. R. H.; Eglinton, G.; Whiting, M. C.; Shaw, B. L. "Organic Syntheses"; Wiley: New York, 1963; Vol. IV, p 404 (footnote 12).

(6) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

0022-3263/83/1948-1139$01.50/0