substituent was placed on the parent transition structure obtained by the 3-21G optimization. The substituent geometry was then optimized, and the relative energies for inward and outward conrotation were calculated. In the case of boryl substitution, the partial optimization agreed quite well with the full optimization. Inward conrotation was preferred by 5.9 kcal/mol in the constrained case and by 5.5 kcal/mol in the fully optimized case. Strongly electron-donating groups (OH, F) prefer to rotate outward. The preference for outward rotation is 14 kcal/mol for OH and 14 kcal/mol for F. Strongly electron-withdrawing substituents (BH_2, CHO) prefer to rotate inward, with formyl substitution giving a preference for inward rotation of 2 kcal/mol. Thus the stereoelectronic effect found for cyclobutenes is predicted to operate in the conrotatory interconversion of pentadienyl cations and cyclopentenyl cations as well.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research and the UCLA Office of Academic Computing for computer time used for these calculations.

Cycloalkenone Synthesis via Lewis Acid Catalyzed Retro Diels-Alder Reactions of Norbornene Derivatives: Synthesis of 12-Oxophytodienoic Acid

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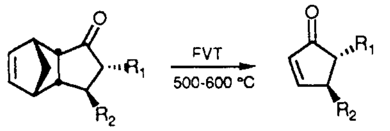
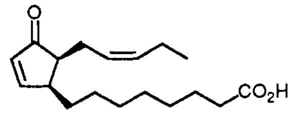
Summary: Norbornene derivatives of type **1** undergo retro Diels-Alder reactions at or below ambient temperature in the presence of methylaluminum dichloride and a reactive dienophile. Application of the [4 + 2] cycloreversion methodology to the synthesis of 12-oxophytodienoic acid **3** is described.

Sir: Retro Diels-Alder reactions have received considerable attention in natural products synthesis in part because the methodology allows for the stereospecific formation or regeneration of an olefin.[1] In particular, the retro Diels-Alder reaction permits the preparation of the thermodynamically less stable 4,5-dialkylcyclopent-2-enones of type **2** (cf. eq 1).[2,3] The use of flash vacuum pyrolysis to effect such cycloreversions has become the standard procedure ever since the introduction of the method by Stork[2] in the early 1970s. We report that substrates such as **1** undergo Lewis acid catalyzed retro Diels-Alder reaction at or below room temperature in the presence of a reactive dienophile. In addition we describe the total synthesis of 12-oxophytodienoic acid (**3**) (12-oxoPDA),[4] an extremely sensitive cyclopentenone widely distributed in plants.



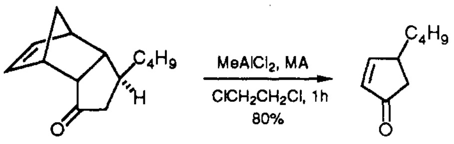
(1)

1 **2**



3

In a preliminary study, a 0.15 M solution of norbornene derivative **4** in 1,2-dichloroethane was treated at ambient temperature with 1.1 equiv of methylaluminum dichloride[5] in the presence of maleic anhydride (MA). After 1 h, an 80% yield of cyclopentenone **5** was obtained. The rearranged cyclopentenone **6** could not be detected. In the absence of added external dienophile to drive the reaction to completion, one gets complex mixtures with only negligible quantities of **5** being produced. For example, after



4 **5**

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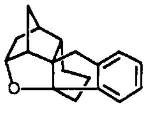
[1] For reviews, see: (a) Ripoll, J.-L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19. (b) Lasne, M.-C.; Ripoll, J.-L. *Synthesis* **1985**, 121. (c) Ichihara, A. *Ibid.* **1987**, 207.

[2] Stork, G.; Nelson, J. G.; Rouessac, F.; Gringore, O. *J. Am. Chem. Soc.* **1971**, *93*, 3091.

[3] For a recent application of flash vacuum thermolysis to the construction of optically active cyclopentenones, see: Klunder, A. J. H.; Huizinga, W. B.; Sessink, P. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 357.

[4] Zimmerman, D. C.; Feng, P. *Lipids* **1978**, *13*, 313. Vick, B. A.; Zimmerman, D. C.; Weisleder, D. *Lipids* **1979**, *14*, 734. Baertschi, S. W.; Ingram, C. D.; Harris, T. M.; Brash, A. R. *Biochemistry* **1988**, *27*, 18.

[5] Triflic acid in the presence of a reactive dienophile will catalyze the retro Diels-Alder reaction. For example, treatment (1 h) of a 0.25 M solution of norbornene derivative **4** in methylene chloride cooled to 0 °C with 6.0 equiv of triflic acid in the presence of 5.0 equiv of *N*-methylmaleimide (NMM) gave rise to a 79% yield of cyclopentenone **5**. In the absence of NMM one gets complex mixtures and extensive decomposition. There are, however, serious limitations to employing triflic acid. In the case of norbornene derivative **14**, exposure of **14** to triflic acid and NMM at 0 °C, as detailed above, leads not to the formation of 2-benzylcyclohexenone, but instead affords the polycyclic ether i, mp 114-115 °C, in 60% yield.



i

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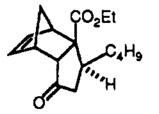
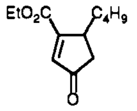
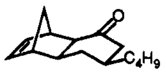
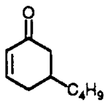
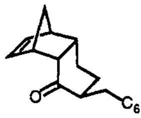
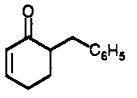
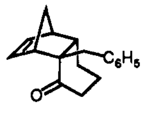
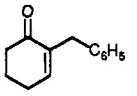
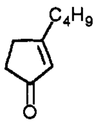
Table I. Retro Diels–Alder Reactions of Norbornene Derivatives[a]

entry	substrate	temp, °C	time, h	product	% yield[b]
1	 **8**	70	1	 **9**	82
2	 **10**	60	1.5	 **11**	86
3	 **12**	55	1.5	 **13**	89
4[c]	 **14**	65	4.5	 **15**	80

[a] All reactions were conducted in 1,2-dichloroethane containing 1.1 equiv of methylaluminum dichloride and 5.0 equiv of maleic anhydride unless indicated otherwise. The 1,2-dichloroethane solution was 0.15 M in substrate. [b] Isolated yields. [c] No maleic anhydride was employed.

prolonged exposure (24 h) to methylaluminum dichloride, cyclopentenone **5** is isolated in only 10% yield along with ca. 35% of recovered starting material and ca. 42% of the exo Diels–Alder adduct **7**.[6] With respect to the nature of the dienophile, maleic anhydride and fumaronitrile have been employed interchangeably, and we find no advantage of one over the other.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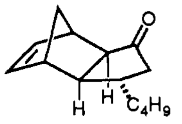
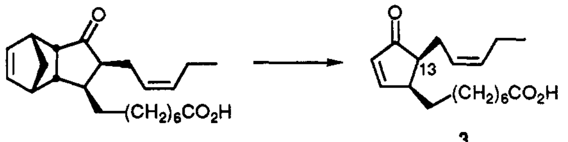
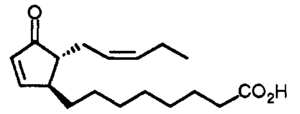
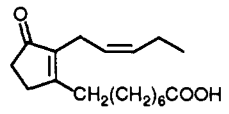

7

The cycloreversion process is applicable to a number of other norbornene derivatives (Table I). All reactions were conducted with methylaluminum dichloride; however, ethylaluminum dichloride is equally effective. Note that in those cases where the resultant cycloalkenone is a poor dienophile, the use of an external dienophile to drive the reaction to completion is not required. For example (entry 4), exposure of a 0.15 M solution of **14** in 1,2-dichloroethane to 1.1 equiv of methylaluminum dichloride at 65 °C for 4.5 h afforded an 80% yield of 2-benzylcyclohexenone.[7]

In order to demonstrate the mildness of the reaction conditions detailed above for effecting retro Diels–Alder reactions, we prepared and subjected **18** to cycloreversion. The anticipated product of [4 + 2] cycloreversion of **18** is 12-oxophytodienoic acid (**3**), the metabolic parent of oxo-2-*cis*-(pent-2(*Z*)-enyl)cyclopentylalkanoic acids including epijasmonic acid. 12-OxoPDA is extremely sensitive to acid and base. Exposure of **3** to acid brings about epimerization at C(13) with formation of the trans isomer **19** of 12-oxoPDA. Prolonged treatment of **3** or **19** with acid or base leads to formation of the thermodynamically more stable cyclopentenone **20**.[4]


18 **3**


19


20

Norbornene **18** was prepared in straightforward fashion via a three-step sequence from the known, enantiomerically pure tricyclo[5.2.1.0^{2,6}]decadienone (**16**).[8] A three-com-

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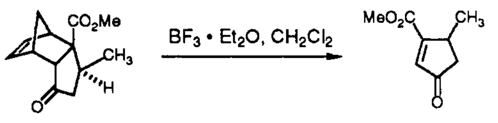
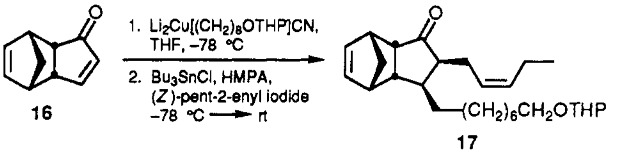
[6] We were surprised to find, after completion of our study, a report in the literature [Marchand, A. P.; Vidyasagar, V. *J. Org. Chem.* **1988**, *53*, 4412] which detailed the synthesis of cyclopentenones via a boron trifluoride etherate mediated [4 + 2] cycloreversion (cf. ii → iii) in the absence of added dienophile. Experiments from our laboratory suggest that, with the exception of 2-substituted cyclohexenones, reactive external dienophiles are required to trap the cyclopentadiene as it is formed so as to drive the cycloreversion reaction to completion. In our hands exposure of ii to 1.1 equiv of boron trifluoride etherate in methylene chloride at ambient temperature for 6 h gave rise to only a 10% yield of cyclopentenone iii.


ii iii

[7] The following experimental employing norbornene derivative **12** serves as a general procedure for the Lewis acid catalyzed retro Diels–Alder reaction. To a homogeneous solution of **12** (60 mg, 0.25 mmol) in 2.0 mL of 1,2-dichloroethane containing maleic anhydride (120 mg, 1.25 mmol) under argon was added, via syringe, 275 μL of a 1.0 M solution of methylaluminum dichloride in hexanes. The reaction was stirred at 55 °C. After 1.5 h, the reaction was cooled to ambient temperature and was quenched with saturated sodium bicarbonate solution. The product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified on 10 g of silica gel. Elution with ether–hexanes (1:9) provided 39 mg (89%) of 6-benzylcyclohex-2-enone, which was identical in all respects with an authentic sample.

[8] Klunder, A. J. H.; Huizinga, W. B.; Halshof, A. M. J.; Zwanenburg, B. *Tetrahedron Lett.* **1986**, *27*, 2543.

ponent coupling process[9] to assemble intermediate **17** (cf. eq 2) followed by cleavage (PPTS,[10] MeOH, 50 °C, 2 h) of the THP ether and oxidation (Jones reagent, acetone, 0 °C, 35 min) of the resultant primary hydroxyl afforded norbornene **18**, $[\alpha]^{25}_D$ +71.2° (*c* 10.0, $CHCl_3$), in ca. 40% overall yield. Treatment of a 0.03 M solution of **18** in 1,2-dichloroethane with 2.5 equiv of ethylaluminum dichloride and 5.0 equiv of fumaronitrile at ambient temperature for 2 h gives rise (60%) to (+)-12-oxophytodienoic acid (**3**), $[\alpha]^{25}_D$ +104.0° (*c* 9.5, $CHCl_3$), whose distinctive ^1H NMR spectrum was identical with a ^1H NMR spectrum of the natural product kindly provided by Professor Harris.[4,11] Indeed, upon brief contact with acid 12-oxoPDA underwent equilibration at C(13) with formation of **19**, which is spectroscopically (^1H NMR) and chromatographically (TLC) quite different from natural 12-oxoPDA.



(2)

Acknowledgment. This investigation was supported by a Public Health Service Research Grant from the National Institute of General Medical Sciences (GM 33605). We thank Professor Thomas Harris for the ^1H NMR spectrum of 12-oxoPDA and Professor Alan Marchand for a generous sample of norbornene derivative ii.

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[9] Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348. Johnson, C. R.; Penning, T. D. *Ibid.* **1986**, *108*, 5655. Corey, E. J.; Niimura, K.; Kinishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

[10] Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

[11] For a recent synthesis of **3**, see: Crombie, L.; Mistry, K. M. *J. Chem. Soc., Chem. Commun.* **1988**, 537.

Discrimination between Amino Acid Amide Conformers by Imprinted Polymers

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Summary: By a molecular imprinting technique based on noncovalent interactions polymers were obtained which selectively discriminate between amino acid amides, different only in a single methyl group, as well as between their enantiomers. The selective recognition is ascribed to a difference in conformation between the print molecules, resulting in recognition sites of different shapes. The sites are able to recognize the amide conformation of the original print molecule.

Sir: The technique of molecular imprinting allows the preparation of polymers containing "tailor-made" recognition sites.[1-11] During the last years we have developed an imprinting technique based on noncovalent interactions.[4-7] Its key steps, outlined in Scheme I, are: (I) mixing of a print molecule (template), an L-amino acid derivative, and methacrylic acid (MAA) in solution, (II) copolymerization of the formed assemblies with a crosslinking monomer (EDMA), (III) removal of the print molecule by simple extraction, and (IV) chromatographic evaluation of the polymer recognition sites by comparing their ability to separate the enantiomers of the substrate and of substrate analogues.

The binding selectivity of imprinted polymers was shown to be influenced by the number of potential interaction sites,[5,6] by their intramolecular distance,[8,9] as well as by the shape[5,10,11] of the print molecule. An important question is to what extent the shape of the print molecule contributes to the polymer selectivity.

This paper reports on the molecular recognition properties of polymers prepared using as print molecules either L-phenylalanine anilide (L-PheNHPh) or L-phenylalanine-*N*-methylanilide (L-PheNMePh), two molecules that should have different amide conformations. To our knowledge this is the first example of imprinted polymers where the recognition properties depend on the confor-

Scheme I

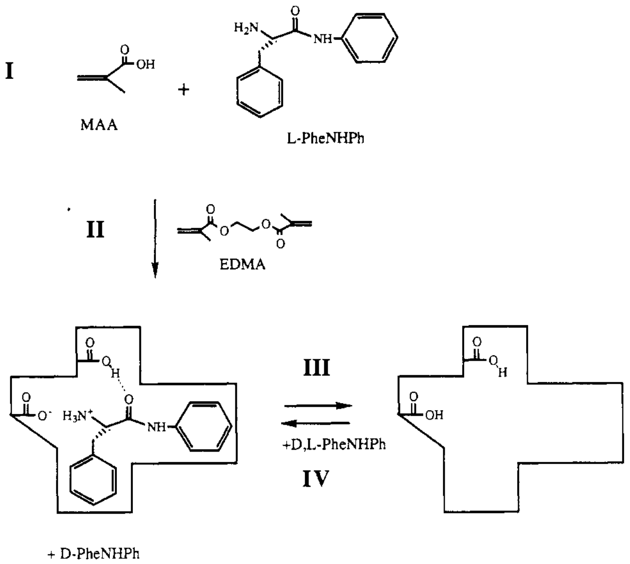

Table I. Chromatographic Data[a] for Polymers Imprinted with either L-PheNHPh or L-PheNMePh[12]

	substrate					
	D- or L-PheNHPh			D- or L-PheNMePh		
polymer	k'_D	k'_L	α (=k'_L/k'_D)	k'_D	k'_L	α (=k'_L/k'_D)
L-PheNHPh	1.57	6.57	4.18	0.98	1.05	1.07
L-PheNMePh	1.24	1.68	1.36	1.05	2.13	2.03

[a] Eluent: 10% (v/v) acetic acid in acetonitrile. Temperature: 23 °C. Flow rate: 0.4 mL/min. Amount applied: 0.2 μmol/g of polymer. k'_D = capacity factor of the D-form. α = separation factor.

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