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Natural product syntheses based on asymmetric Diels–Alder reactions

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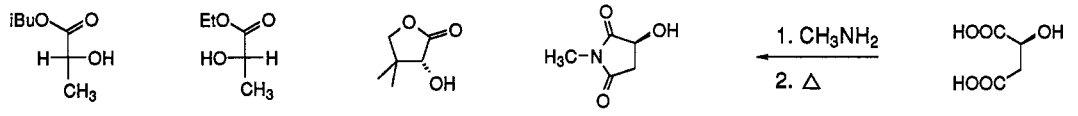
Abstract - (R)-Pantolactone, (S)-ethyl lactate and other α-hydroxy-carboxylic acid derivatives are effective chiral auxiliaries for large-scale asymmetric Diels-Alder additions of enoates. Mechanistic aspects and preparations of intermediates for EPC-syntheses of carbocyclic nucleoside analogs, prostaglandins and other biologically active compounds are described.

INTRODUCTION

Excellent progress has recently been achieved in the development of chiral auxiliaries for asymmetric Diels-Alder (ADA) reactions (ref. 1). Work of this group has shown that enoates of α-hydroxycarboxylic acid derivatives are very useful chiral dienophiles. (R)- and (S)-lactates **1** and **2** (ref. 2), (R)-pantolactone (**3**) (ref. 3) and (S)-N-methyl-2-hydroxysuccinimide (**4**) were found to be particularly effective auxiliaries.



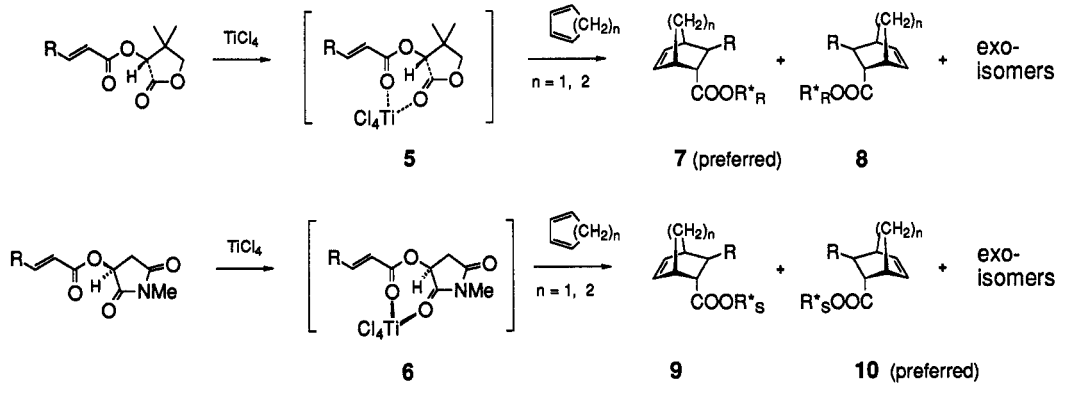
1 (R) **2** (S) **3** (R) **4** (S)

1 - **3** are large-scale commodities. The imide **4** is available in one step from (S)-malic acid. The combination of low cost, ease of enoate formation and hydrolysis, and ready cristallization of derivatives of **3** and **4** allows practical large-scale preparations (>100 g) of numerous building blocks useful for EPC-syntheses of biologically active compounds.

LEWIS ACID CATALYZED REACTIONS—FUNDAMENTALS

Our mechanistic rationale, inter alia based on crystal structures of enoate/Lewis acid complexes (refs. 4,5), for description of titanium tetrachloride catalyzed reactions of enoates of the auxiliaries **3** and **4** is presented in Scheme 1 for the special case of cyclic dienes (ref. 6). Essential features of the reactive chelate complexes **5** and **6** are syn-enoate conformations and diastereoface-selective shielding of the enoate group by the $TiCl_4$ moiety. Quite generally, Diels-Alder adducts were obtained with diastereoselectivity of ca. 97:3 (**7**:**8** or **10**:**9**) and pure major isomers resulted after recrystallization.

Scheme 1



5 **7** (preferred) **8**

6 **9** **10** (preferred)

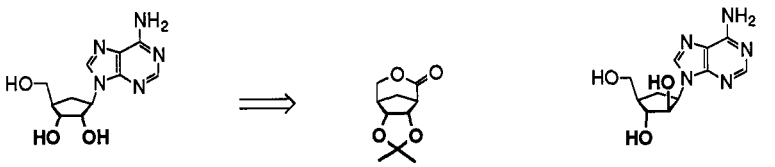
Earlier work in the area of ADA reactions was aimed at high degrees of stereoselectivity. Today, high reactivity of the dienophile and practicality are increasingly recognized as equally important features. Touchstones for assessing these aspects are the reactions of trans-crotonates with cyclopentadiene and of acrylates with cyclohexadiene, combinations of low reactivity. Carried out according to Scheme 1, no difficulties were encountered (ref. 7).

11 **12** **13** **14** **15** **16** R = H **17** R = CH_3

Some of the carboxylic acids obtained by saponification (LiOH, THF/H_2O) of adducts **7** or monocyclic analogs are shown above. ß-Bromoacrylates (R=Br, Scheme 1) are saponified with concomittant elimination to give **14**. Similarly, treatment with NaOBn/BnOH yields the ß-addition product **15**. All these compounds are useful for EPC-syntheses of natural products (ref. 8).

CARBOCYCLIC NUCLEOSIDE ANALOGS

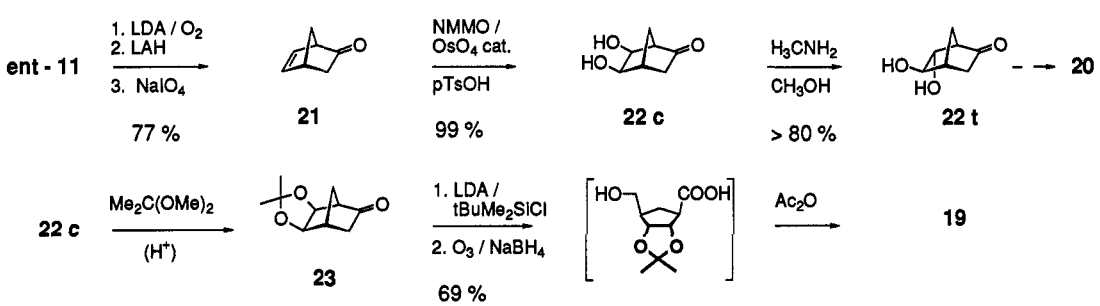
Some natural and unnatural carbocyclic analogs of nucleosides display interesting physiological effects (antiviral, antibiotic, and antitumor activities) (ref. 9). Recent work of our group has been directed at synthesizing compounds of this class via enantiomerically pure Diels-Alder adducts. Here we report a short synthesis of Ohno's lactone (**19**) which was previously transformed into (-)-aristeromycin (**18**) (antibiotic) (ref. 10). In the course of this work, an intermediate suitable for a synthesis of the antiviral agent cyclaradine (**20**) (ref. 11) was also obtained.



18 (-) - aristeromycin **19** Ohno's lactone **20** cyclaradine

(+)(R)-5-Norbornene-2-carboxylic acid (**ent-11**) yields (1R)-5-norbornen-2-one (**21**) via a simple three-step sequence (ref. 12)(Scheme 2). Our synthetic plan called for cis-dihydroxylation of the double bond and subsequent oxidative cleavage of the C2-C3-bond. To our surprise, reaction of **21** with osmium tetroxide/N-methylmorpholine N-oxide gave mainly the trans-addition product **22t** (ratio **22t**:**22c** ca. 4:1). The source of this anomaly became clear when it was found that **22c** rearranges to **22t** upon treatment with base, obviously via retro-aldol reaction. As a consequence, the hydroxylation was carried out with one equiv. of p-toluenesulfonic acid added to the standard agent. This procedure indeed furnished **22c** in quantitative yield. Treatment of **22c** with methylamine in methanol gave **22t** in high yield. Transformation of **22c** into Ohno's lactone, via the acetal **23** and ozonization of its silyl enol ether, was uneventful. The total yield of **19** from 5-norbornene-2-carboxylic acid was 54 %. A route from **22t** to cyclaradine (**20**) is currently being worked out.

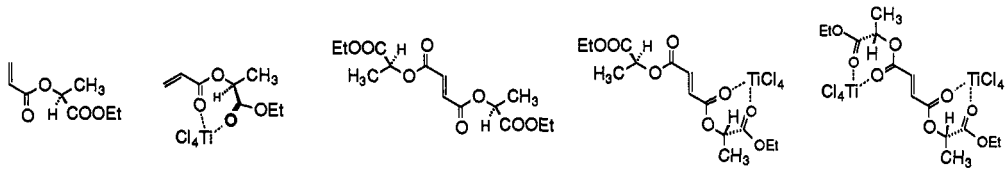
Scheme 2



NON-CATALYZED AND LEWIS ACID CATALYZED REACTIONS OF FUMARATES

In view of their potential experimental simplicity and broad range of applications, non-catalyzed ADA additions are of great interest. However, until very recently little success was achieved with esters. In contrast, the acrylate **24** of (S)-ethyl lactate (**2**) reacts diastereoselectively with cyclopentadiene at 0 °C in hexane (endo-add.: 80:20, exo-add.: 85:15)

(ref. 2). The (typically) low endo-exo ratio of 1.7 prevents direct preparative use of these results. But it was of interest to examine corresponding fumarates which cannot give rise to endo-exo isomers and, furthermore, were expected to show synergistic activity of their auxiliary groups and, in consequence, a higher level of selectivity than acrylates (cf. refs. 1a, 4). The fumarate **26**, displaying diastereoselectivity of 98:2 with cyclopentadiene in n-hexane (Scheme 3), is indeed the more selective dienophile. It is assumed that the reaction proceeds via the C_2-symmetric species **26** with anti-enoate conformation (cf. Formula) for which attack from the more accessible back-face is favored.



24 **25** **26** **27** **28**

For $TiCl_4$-catalyzed reactions of the acrylate **24**, which yield preferred products of opposite configuration compared to the non-catalyzed reaction, the complex **25** with syn-enoate conformation is postulated as reactive species (cf. Scheme 1). On extending this model to the fumarate **26** one would expect the 1:1 complex **27** with syn- and anti-enoate conformations as reactive species, and therefore antagonistic action of the auxiliary groups, and/or the 2:1 complex **28** with syn-enoate conformations on both sides, and therefore synergistic action of the auxiliary groups. For differentiation of these complexes, **26** was allowed to react with cyclopentadiene using various $TiCl_4$: **26** ratios and the products (Scheme 3) were analyzed by HPLC. We interpret the results of this series of experiments (Fig. 1) as follows: **27** determines the mode of reaction at low $TiCl_4$: **26** ratios (A), hence the non-selective reaction. In the range B, competition of the complex **28** becomes noticeable, which in range C finally dominates and yields the ester **29b** with 95:5 selectivity (ref. 4).

Results obtained with the fumarate of (R)-pantolactone, **30**, are displayed in Scheme 4. Compared to **26**, the fumarate **30** yields Diels-Alder adducts of opposite configuration due to inverse chirality sense of the HO-C-CO moieties of 2 and 3. Thus, for an extensive variety of chiral trans-dicarboxylic acids both enantiomers are accessible via non-catalyzed reactions. Lewis acid promoted reactions of the fumarate **30** also proceed with high selectivity when $EtAlCl_2$ is employed in excess. For a reason not yet understood, in conjunction with **30**, $EtAlCl_2$ is more effective than $TiCl_4$.

Diels-Alder reactions with the inexpensive fumarates **26** and **30** are of interest for EPC-syntheses of physiologically active compounds - e.g., the (2S,3S)-5-norbornene-2,3-dicarboxylic acid readily obtainable (ref. 1a) from adducts **29b** or **31a** is a starting material for the ICI prostaglandin synthesis (ref. 13). Another, less obvious entry into the prostaglandin series is shown in Scheme 5. Key step is the decarboxylative 1,3-elimination of the easily prepared iodolactone **35** which furnishes the nortricyclene **36** in quantitative yield. From the lactone **36**, straightforward synthetic tactics leads to the Corey-Sutherland intermediate **39** (ref. 13) and the syn-isomer **38** (76 % yield from **35**) which opens avenues to a large variety of important natural products (cf. ref. 14).

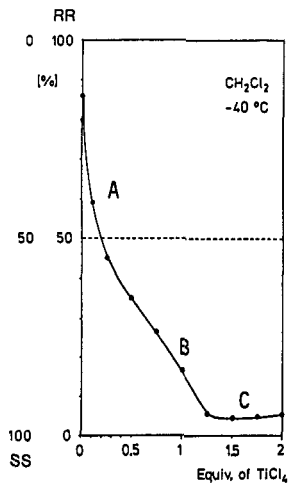
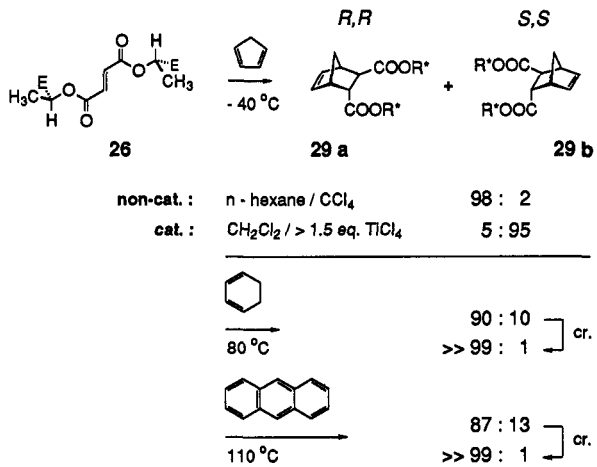
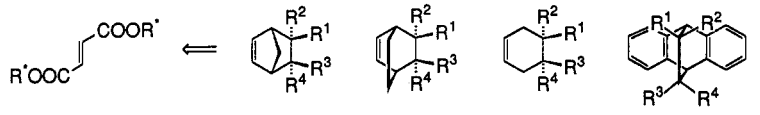


Fig. 1. Dependence of the diastereoselectivity of the reaction of **26** with cyclopentadiene on the ratio $TiCl_4$:**26**.

Scheme 3



Scheme 4

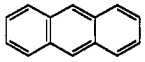


30 **31** **32** **33** **34**

R*OH = (R) - pantolactone

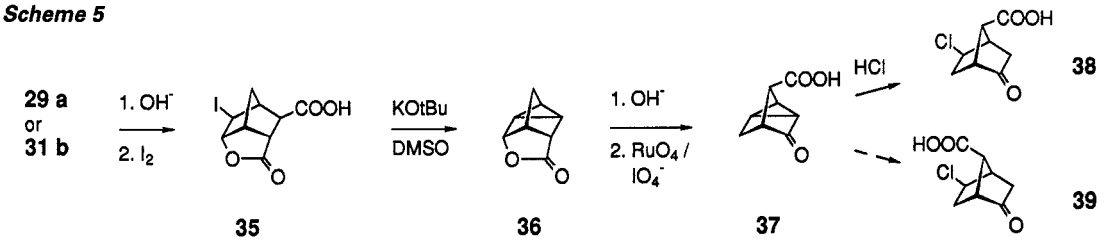
a $R^1 = R^4 = H$, $R^2 = R^3 = COOR^*$

b $R^1 = R^4 = COOR^*$, $R^2 = R^3 = H$

Non-catalyzed Solvent: carbon tetrachloride				**Catalyzed:** 4 equiv. of $EtAlCl_2$ Solvent: methylene chloride			
Diene	Temp. [°C]	a:b[b]	Y. [%]	Temp. [°C]	a:b	Y. [%][c]
	0	94.5:5.5	98	-30	7.5:92.5	90
		cr >>99 :1	80		cr << 1 :99	60
	80	88 :12	95	-24	3 :97	90
		cr >>99 : 1	61		cr << 1 :99	60
	80	70 :30	100	-24	3 :97	90
		cr >>99 : 1	60		cr << 1 :99	50
	110[a]	97 : 3	95	0	4 :96	80
		cr >>99 : 1	82		cr << 1 :99	61

(a) Solvent: toluene; (b) cr: after crystallization; (c) yields are not optimized.

Scheme 5



29 a or **31 b** → 1. OH^-, 2. I_2 → **35** → KOtBu, DMSO → **36** → 1. OH^-, 2. RuO_4 / IO_4^- → **37** → HCl → **38** / **39**

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