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N-SUBSTITUTED HYDROXYSUCCINIMIDES FROM (S)-MALIC ACID AS NEW REAGENTS FOR ASYMMETRIC DIELS-ALDER ADDITIONS TO ENOATES

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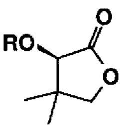
Summary: (S)-N-Methyl-2-hydroxysuccinimide, easily available from natural (S)-malic acid, supplements the previously introduced (R)-pantolactone as chiral auxiliary for asymmetric Diels-Alder reactions of enoates, but yields products of opposite configuration. Practical large-scale preparations of enantiomer pairs of synthetically important Diels-Alder adducts, including adducts from crotonates, are described.

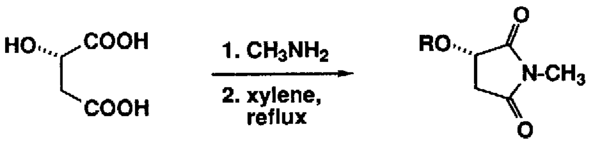
Recently we reported[1] that (R)-pantolactone (1) is an excellent chiral auxiliary for Lewis acid catalyzed asymmetric Diels-Alder reactions of enoates. The success of this reagent is related to the following characteristics:

- Commercial availability (production of the vitamin pantothenic acid)[2];
- High degree of diastereoselectivity (ca. 97:3) independent of reaction temperature;
- Diels-Alder adducts are crystalline and the respective major isomers can be obtained diastereomerically pure by recrystallization (HPLC monitoring);
- A low degree of steric bulk and ease of ester formation, usually by standard H^+-catalyzed esterification (examples: see below), as well as hydrolytic ester cleavage (LiOH, THF/H_2O) free of racemization or epimerization.

So far only reactions of the acrylate **2a** were described. In this report, we demonstrate that the less reactive crotonate **2b** also gives excellent results. Furthermore, the enantiomer of 1 is not a commodity; therefore, a complement of (S)-configuration was required. We now report that (S)-N-methyl-2-hydroxysuccinimide (3) displays properties very similar to those of (R)-pantolactone, but induces selectivity of opposite configurational sense. Preparation of the new auxiliary 3[3] and its esters 4[4] is extremely simple:



1 R = H
2 a-c

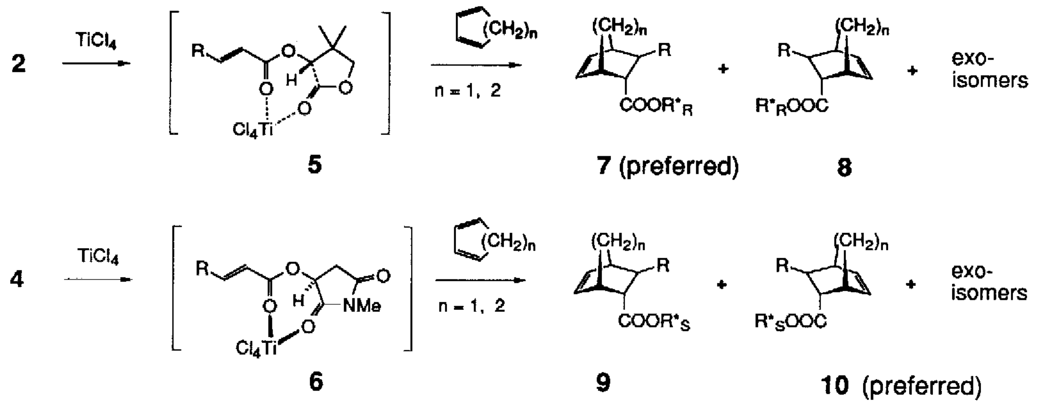


(-)(S)-malic acid

3 R = H
4 a-c

a R = $OC{-}CH{=}CH_2$ **b R =** $OC{-}CH\overset{E}{=}CH{-}CH_3$ **c R =** $OC{-}CH\overset{E}{=}CH{-}Br$

The development of the new chiral auxiliaries was based on the assumption that, similar to the case of enoates of lactates[5], esters 2 and 4 would form chelate complexes 5 and 6, respectively, with titanium tetrachloride. These complexes are expected to possess a syn enoate conformation with one enoate face selectively shielded by the $TiCl_4$ moiety:



The results obtained support this proposal. First, reactions of the acrylates **2a** and **4a** with cyclopentadiene were investigated in order to assess the influence of reaction conditions on diastereoselectivity. The results, cf. Table 1 and Fig. 1, show that reactions of both acrylates yield a very high level of diastereoselection that is almost independent of the reaction conditions which indicates chelate complexes of high stability. With respect to preparative applications it is important to note that reactions can be run at concentrations as high as 0.5 mol/L. This is a very important point because most of the known asymmetric Diels-Alder reactions require impractical concentrations of 0.1 mol/L or less. Temperature is another important variable. In contrast to reactions of enoates of other auxiliaries, diastereoselectivities of the reactions of enoates 2a and **4a** are almost independent of temperature (Fig. 1B). However, endo-exo selectivity, typically[1a], decreases with increasing temperature (Table 1). It is for that reason that running additions at low temperature is advantageous.

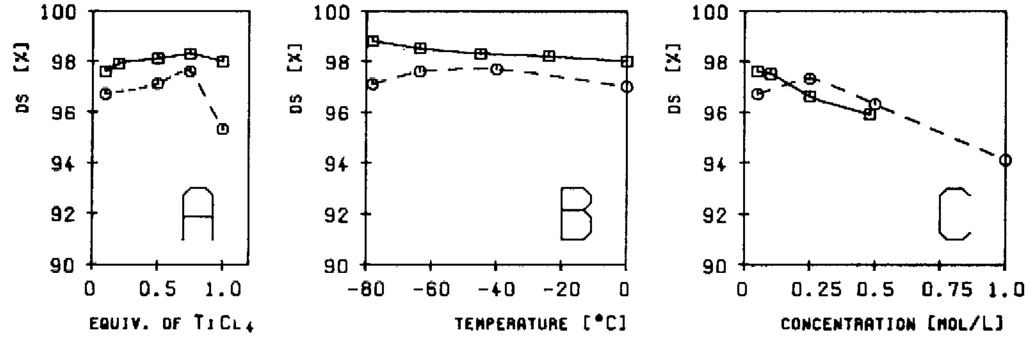
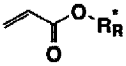
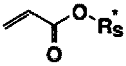
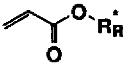
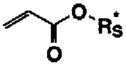
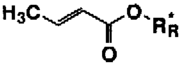
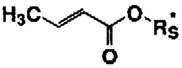
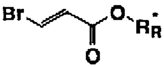
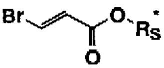


Fig. 1. Dependence of diastereoselectivity (DS[1a]) of titanium tetrachloride catalyzed reactions of **2a** (—○— —○—) or **4a** (—□——□—) with cyclopentadiene on reaction conditions

A: c = 0.05 mol/L, CH_2Cl_2/n-hexane (2a 1:1, **4a** 4:1), **2a**: -63 °C, **4a**: -45 °C;
B: c = 0.05 mol/L, 0.75 equiv of $TiCl_4$, CH_2Cl_2/n-hexane (2a 1:1, **4a** 4:1);
C: 0.1 equiv. of $TiCl_4$, -40 °C, CH_2Cl_2/n-hexane (**2a** 1:0, **4a** 4:1).

Table 1. Preparative asymmetric Diels-Alder reactions with enoates of (R)-pantolactone (1 = R_R*-OH) and (S)-N-methyl-2-hydroxysuccinimide (3 = R_s*-OH); Lewis acid: $TiCl_4$, Solvents: methylene chloride (M) and l. b. petroleum ether (PE).

Dienophile	Diene	Reaction conds. [a]	Temp. [°C]	Endo-exo ratio	Diastereosel.[b] 7:8 or 10:9	Y. [%][c]
		(0.7) M/PE 1:1 (0.1) M/PE 1:1	- 64 - 10	35:1 20:1	98:2 97:3 >>99:1 cr.	81
		(0.7) M/PE 4:1 (0.2) M/PE 4:1	- 78 - 10	52:1 20:1	99:1 97:3 >>99:1 cr.	86
		(0.75) M/PE 1:1	0	120:1	94.5:5.5 99.5:0.5 cr.	85
		(0.75) M	0	82:1	97:3 >>99:1 cr.	89
		(0.75) M	- 24	14:1	97.5:2.5 >>99:1 cr.	74
		(0.75) M	- 24	13:1	97:3 >>99:1 cr.	62
		(0.8) M	- 24	54:1	98:2 >99:1 cr.	78
		(0.7) M	- 24	38:1	98:2 >>99:1 cr.	70

[a] Values within brackets: equivalents of $TiCl_4$.

[b] Determined by HPLC: Merck LiChrosorb (silica) Si 60, 5 µm, mixtures of petroleum ether/ ethyl acetate of appropriate eluotropicity, RI detection, diastereomer ratios are based on ratios of peak areas; >>99:1 means: the minor isomer (with known location in the chromatogram) was not detected;
cr.: diastereomer ratio and yield after recrystallization.

[c] Yield of diastereomerically pure major adduct after purification by recrystallization.

Results obtained with acrylates and cyclopentadiene are representative with respect to diastereoselectivity. However, they are not significant concerning the scope of an auxiliary's applicability which is also defined by enoate reactivity. For demonstration of this we have selected Diels-Alder reactions which previously failed with ester dienophiles because of competing polymerization: the combinations acrylate/1,3-cyclohexadiene[6] and crotonate/cyclopentadiene[7]. In the present case no difficulties were encountered (cf. Table 1).

The results displayed in Table 1 demonstrate that the enoates **4**, of the new auxiliary, perform even better than the esters 2 of (R)-pantolactone. Purification by crystallization and mild saponification (cf. introduction) produced the pure enantiomeric acids **11-13** and **ent-11-ent-13** (yield >90 %) which are useful chiral synthons. Not unexpectedly, saponification of the adduct of the ß-bromoacrylate **2c** was accompanied by elimination and gave the carboxylic acid **14**, obviously a valuable chiral building block[8,9]. Similarly, treatment with NaOBn/BnOH furnished the adduct **15**.


11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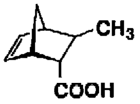
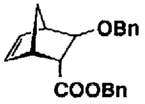

13


14


15 (Bn = CH_2Ph)

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1. (a) T.Poll, A.Sobczak, H.Hartmann, G.Helmchen, Tetrahedron Lett. 1985, 3095; (b) a review including experimental procedures on asymmetric Diels-Alder reactions of enoates: G.Helmchen, R.Karge, J.Weetman in R.Scheffold (Ed.), Modern Synthetic Methods 1986, vol. 4, p. 262-306, Springer, Heidelberg 1986.
2. This fact appears not to be widely known. The production scale of (R)-pantothenic acid is estimated to be ca. 5,000,000 kg/year: Ullmanns Encyklopädie der technischen Chemie, 4th ed., Verlag Chemie, Weinheim 1983, vol. 23, p. 697.
3. **Preparation of the reagent** (S)-3: 13.41 g (0.10 mol) of (-)(S)-malic acid is dissolved (warming) in 25 ml of ethanol (95 %). 50 ml of an ethanolic 2 N solution of CH_3NH_2 is then slowly added. After cooling in an ice bath the precipitated salt is isolated by suction. A suspension of the salt in 500 ml of xylene is heated to reflux (Dean/Stark head) until water evolution ceases (ca. 4 h). The xylene solution is concentrated in vacuo until crystallization commences. After completion at 0 °C the product is filtered off and recrystallized from ethyl acetate/n-hexane: 8.4 g (65 %), mp 79.5-80 °C, $[\alpha]_D$ -81.8 ° (c 3.5, 95 % ethanol).
4. **Preparation of esters 2 and 4:** Acrylates were prepared as previously described (ref. 1b) (yield >80 %). All other enoates were obtained by standard acid catalyzed esterification (pTsOH or Dowex 50 cation exchange resin, benzene or toluene, reflux, Dean/Stark head).
5. T.Poll, J.O.Metter, G.Helmchen, Angew.Chem.Int.Ed.Engl. 24, 112 (1985).
6. O.Cervinka, O.Kriz, Coll.Czechoslov.Chem.Commun. 33, 2342 (1968).
7. W.Oppolzer, C.Chapuis, D.Dupuis, M.Guo, Helv.Chim.Acta 68, 2100 (1985).
8. E.J.Corey, M.Shibasaki, K.C.Nicolaou, C.L.Malmsten, B.Samuelsson, Tetrahedron Lett. 1976, 737.
9. A direct synthesis of **14** by Lewis acid catalyzed reaction of the ester $HC{\equiv}C\text{-}COOR_R^*$ with cyclopentadiene gave a very low level of diastereoselectivity; for similar results see: D.A.Evans, K.T.Chapman, J.Bisaha, J.Am.Chem.Soc. 110, 1238 (1988).

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