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Asymmetric synthesis of β-hydroxyesters by aldol type condensation of enantiomerically pure *t*-butyl *p*-tolyl sulfinyl acetate: unexpected substituent effect on the absolute configuration of the product

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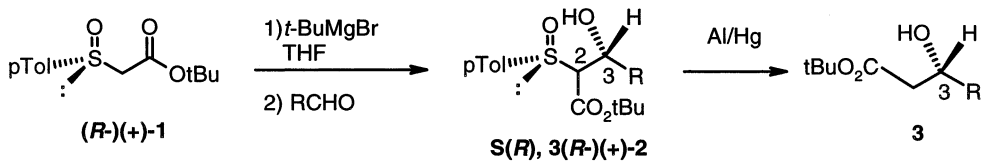
Abstract—Aldol type condensation of enantiomerically pure *t*-butyl *p*-tolyl sulfinyl acetate was shown to give the opposite configuration at the hydroxylic center in the case of an α,β-unsaturated aldehyde, a result which is in sharp contrast with literature results. The absolute configurations of the aldol products were determined by X-ray crystallography.

Several years ago, we reported a very efficient asymmetric synthesis of β-hydroxyacids based on the aldol type condensation of *R*-(+)-*t*-butyl *p*-tolyl sulfinyl acetate on carbonyl compounds (Scheme 1).[1–5]

The sulfinyl acetate enolate has to be made with a Grignard as a base, *t*-BuMgBr, the magnesium chelating effect being important to quench the adduct with carbonyl compounds. It was shown by many examples that the diastereoselection was very high, giving mainly one diastereomer of **2**. After desulfurization, the resulting β-hydroxyester had always the configuration shown in Scheme 1, in 85–95% ee, determined by chemical correlation. Many applications to natural-product synthesis confirmed this assignment.[4–8] The absolute configuration of C2 in the first adduct **2** was determined only in the case of benzaldehyde and shown to be (*R*,*R*,*R*) from the (*R*)-α-sulfinyl acetate **1**.[3] The C2–C3 relative configuration assignment was carried out via a pyrolytic sulfoxide *cis* elimination of the corresponding acetate derivative of **2** (R = Ph). An empirical model, based on the stereochemical results shown in Scheme 1, was proposed in order to predict the configuration at the hydroxylic center.[3] In many applications the absolute configuration of the second created chiral center (C2) was not determined and was assumed to be the same as in the case of the condensation of benzaldehyde. However, a recent report[12] showed a different mechanism for the pyrolytic sulfoxide elimination in type **2** substrates: intermediate formation of a vinylic sulfoxide. This result prompted us to control the configurations of the type **2** adducts.

We report in this paper that the configuration of the hydroxylic center, which depends in many cases only on the absolute configuration at sulfur, can also depend, in a few cases, on the aldehyde substituent R. We describe here the cases of α,β-unsaturated aldehydes.



Scheme 1.

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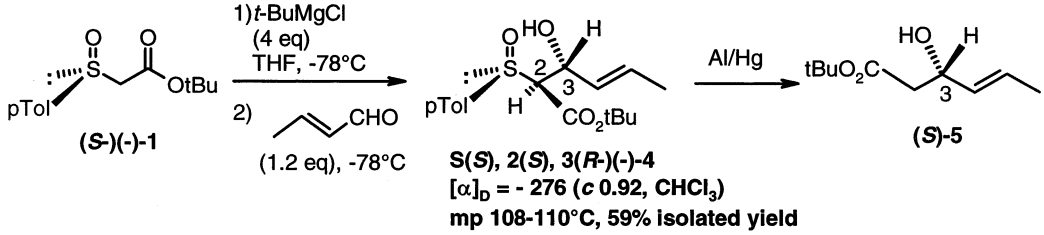
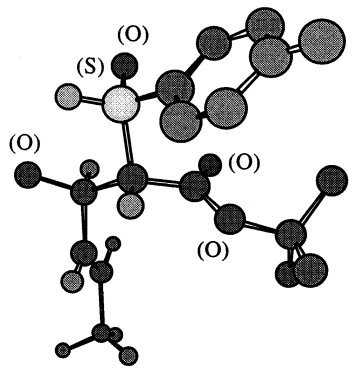


Scheme 2.



Scheme 3. Computer-generated drawing of (–)-**4** derived from X-ray coordinates.

It had already been shown that α,β-unsaturated aldehydes react with chiral sulfinyl acetate to give, after desulfurization, the corresponding β-hydroxyesters in high ee. In the final steps of the synthesis of maytansine, Corey[6] used this aldol type condensation with phenyl (*R*) *p*-tolyl sulfinyl acetate (instead of the *t*-butyl ester) and determined the absolute configuration of the hydroxylic center by comparison with the natural product. The result was consistent with our empirical rule,[3] predicting the *R* configuration for the hydroxylic center from the *R* sulfoxide.

In our program on the total synthesis of natural products we had to prepare the β-hydroxyester **5**, but in the (*R*) configuration. According to our previous results[2–5] this can be done by condensation of the sulfinyl acetate (–)-(*S*)-**1** on *trans* crotonaldehyde. For this reaction we used the usual conditions with only two modifications:[11] *t*-BuMgCl instead *t*-BuMgBr in only 4 equiv. excess, and the main adduct **4** was isolated only by crystallization, thereby avoiding any chromatographic purification (Scheme 2). The diastereoselectivity of the reaction was determined by ^{1}H NMR on the crude product: 64% yield of the main isomer (59% isolated yield) and two other unidentified diastereomers in 21 and 15% yield, respectively.

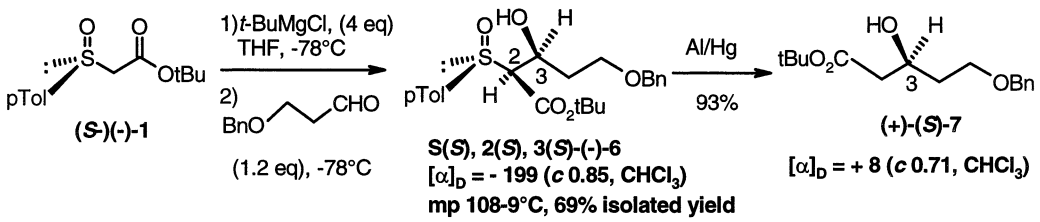
The absolute configuration of the main isomer (–)-**4** was shown to be S(*S*),2(*S*),3(*R*) by X-ray crystallography (Scheme 3), an unexpected result with the opposite configuration at the hydroxylic center with respect to our previous report with benzaldehyde (and also in other synthetic applications): the (*R*) sulfinyl ester leading to the S(*R*),2(*R*),3(*R*) configuration for the main isomer (80% de). Therefore, after desulfurization, the corresponding β-hydroxyester **5** had the (*S*)-configuration.

In addition, we applied this condensation to 3-benzyloxypropanal under exactly the same experimental conditions used for crotonaldehyde, including crystallization of the main isomer (–)-**6** (90% de by ^{1}H NMR for the crude product) (Scheme 4).

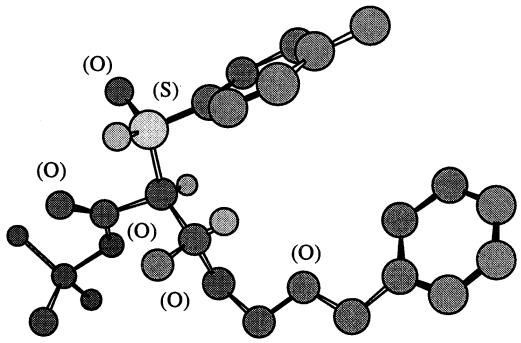
The absolute configuration of the main isomer obtained from the (*S*)-sulfinyl ester was assigned by X-ray analysis (Scheme 5) and shown to be S(*S*),2(*S*),3(*S*), in agreement with our previous results. In addition, after desulfurization, (–)-**6** afforded the known (+)-(*S*)-β-hydroxyester (+)-**7**.[9,10]

These results clearly identified the absolute configurations of the two newly created chiral centers in this aldol type condensation. Finally, starting from the (+)-(*R*)-sulfinyl ester **1** and benzyloxypropanal, we obtained the enantiomer of **6** [60% yield, $[\alpha]_D = +195$ (*c* 1, $CHCl_3$, mp 108–110°C)], which gave the enantiomer of **7** [86% yield, $[\alpha]_D = -7.6$ (*c* 1.6, $CHCl_3$)] after desulfurization.

In conclusion this paper reports the first exception to the empirical rule proposed to predict the absolute configuration of the β-hydroxyester obtained by aldol type condensations with aldehydes. This unexpected result, established by X-ray analysis, was obtained in



Scheme 4.



Scheme 5. Computer-generated drawing of (−)-**6** derived from X-ray coordinates.

the case of an α,β-unsaturated aldehyde. It was also shown by X-ray analysis that in the absence of the double bond the configuration was in agreement with our previous statement. It is important to note that in the case of the maytansine synthesis, which was also an α,β-unsaturated aldehyde, the absolute configuration was in agreement with the empirical rule. The difference could be due to either the larger steric hindrance of the aldehyde used in the maytansine synthesis or to the use of the phenyl instead of the *t*-butylsulfinyl ester.

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Typical aldolization procedure: To (−)-S(*S*)-*t*-butyl *p*-tolylacetate (−)-**1** (4.28 g, 17.4 mmol, 1 equiv.) in THF (160 mL) was added at −78°C a solution of *t*-butylmagnesium chloride (4 equiv.) in ether. After 40 min the crude *trans*-crotonaldehyde (1.65 mL, 19.9 mmol, 1.15 equiv.) was added dropwise to the slurry and stirring was continued for 2 h (the temperature rose to −25°C) until no starting material was detected by TLC. The reaction was then quenched with satd NH_4Cl (50 mL), diluted with water (50 mL) and acidified to pH 1 with 20% H_2SO_4. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to obtain a crude oily product. Crystallization in an ether–hexane mixture gave a first crop of (−)-**4** as white needles (3.2 g, 59%). Mp = 108–110°C, $[\alpha]_D = -276$ (*c* 0.92, $CHCl_3$).
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.46 (AA′BB′, 4H, $J = 8$ Hz, $\Delta\nu = 51$ Hz), 5.82 (dqd, 1H, 2H, $J_{2,3(trans)} = 15$ Hz, $J_{2,1} = 6$ Hz, $J_{2,4} = 1$ Hz), 5.46 (ddq, 1H, $J_{3,2(trans)} = 15$ Hz, $J_{3,4} = 6$ Hz, $J_{3,1} = 1.5$ Hz), 4.38 (m, 1H), 3.41 (d, 1H, $J = 5.5$ Hz), 3.24 (broad d, 1H, $J = 8$ Hz), 2.42 (s, 3H), 1.71 (dd, 1H, $J_{1,2} = 6$ Hz, $J_{1,3} = 1.5$ Hz), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 166.9, 142.7, 139.2, 130.5, 130.3, 129.6, 84.3, 75.8, 71.0, 28.6, 22.1, 18.7.
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