Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1641–1644

TETRAHEDRON: *ASYMMETRY*

A new highly enantioselective synthesis of both (*R*)- and (*S*)-2-mercaptosuccinic acids

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Received 3 March 1998; accepted 31 March 1998

Abstract

(*R*)- and (*S*)-2-Mercaptosuccinic acids **4** were prepared in five steps in >96% ee and 49–52% overall yield via a new efficient synthesis starting from commercially available L- and D-aspartic acids.

2-Mercaptosuccinic acid is an important chiral multifunctional intermediate in organic synthesis. It has been widely employed in the synthesis of various biologically active sulfur containing compounds such as the antileukemic spiro[indoline-3,2′-thiazolidine]-2,4′-diones,[1] and the antimicrobial[2] and antitubercular[3] 4-thiazolidinones. More recently, 2-mercaptosuccinic acid has been used as a building block in the synthesis of novel polyanionic inhibitors of human immunodeficiency virus and other viruses,[4] and as a starting material in the synthesis of isocysteine, an important non-proteinogenic amino acid in a potent peptide inhibitor of stromelysin.[5] In addition, the sodium salt of the anionic Au(I) complex of 2-mercaptosuccinic acid is an effective antiarthritic drug.[6] In all of these studies, racemic 2-mercaptosuccinic acid was used, undoubtedly due to the lack of availability of its optically pure enantiomers.

Several methods have been reported for the preparation of 2-mercaptosuccinic acid in enantiomerically enriched forms. Free radical addition of thioacetic acid to enantiomerically pure menthyl maleate or fumarate followed by saponification of the resulting adducts afforded 2-mercaptosuccinic acid. However, the enantiomeric excess was poor (4–21% ee).[7] The asymmetric induction was improved to some degree (up to 30–37% ee) by using amine-based chiral auxiliaries instead of menthol.[8] In a more encouraging approach, freshly prepared cesium thioacetate was reacted with diethyl (*S*)-2-mesylmalate in DMF for 5 days at −20°C to give diethyl (*R*)-2-acetylthiosuccinate in 100% ee. However, significant racemization occurred in the subsequent hydrolysis, affording (*R*)-2-mercaptosuccinic acid in only 59% ee.[9] In addition, 2-mercaptosuccinic acid was prepared in an early report from xanthosuccinic acid with undetermined enantiomeric excess.[10] In a program of our combinatorial drug discovery, we required an

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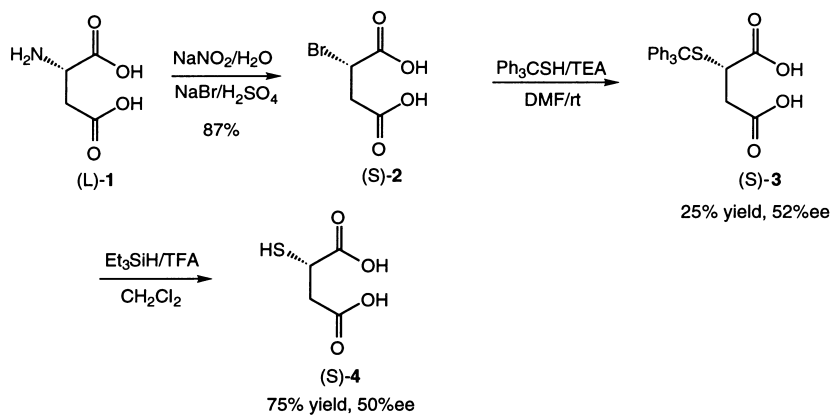
0957-4166/98/$19.00
PII: S0957-4166(98)00149-9

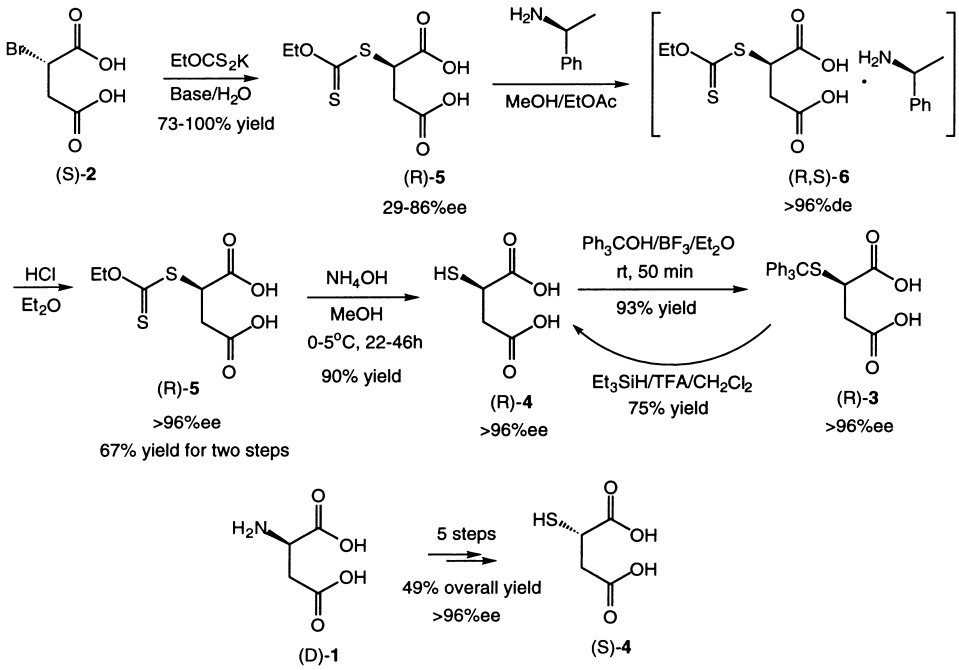
easy access to large amounts of both enantiomerically pure (*R*)- and (*S*)-mercaptosuccinic acids. Herein, we describe an efficient synthesis of both of these compounds in high enantiomeric excess.

Considering the ease with which the α-chiral center is racemized during the conventional hydrolysis of diethyl α-acetylthiosuccinate to 2-mercaptosuccinic acid[9] and the sensitivity to oxidation of free mercaptans in general, we decided to choose α-protected thiosuccinic free acid as the penultimate intermediate en route to 2-mercaptosuccinic acid. Our initial focus was on the preparation of α-tritylthiosuccinic acid from the readily available L-aspartic acid **1** (Scheme 1). Thus, treatment of **1** with sodium nitrite in water, using a modified procedure, afforded (*S*)-bromosuccinic acid **2** in 87% yield.[11] Reaction of (*S*)-**2** with triphenylmethyl mercaptan in DMF at room temperature in the presence of triethylamine gave (*S*)-tritylthiosuccinic acid **3** in 25% yield and 50% ee.[12,13] Noteworthy is that the configuration of the α-chiral center is retained due apparently to the neighboring group participation of the adjacent carboxylic group. Subsequent deprotection of (*S*)-**3** occurred smoothly with Et_3SiH/TFA[14] giving (*S*)-**4** in 75% yield without racemization. The enantiomeric excess of (*S*)-**3** could be improved to 70% ee by generating the mercaptan anion with NaH and carrying out the reaction at lower temperature (−60°C). However, attempts to further upgrade the optical purity of **3** by either modifying the reaction conditions or by partial resolution with chiral non-racemic amines such as benzylmethylamine, quinine, etc., were unsuccessful.



Scheme 1.

We then turned our attention to ethylxanthosuccinic acid **5** as the penultimate intermediate to mercaptosuccinic acid (Scheme 2). Thus, reaction of (*S*)-**2** with the commercially available potassium ethylxanthate in water gave (*R*)-**5** in almost quantitative yield and 70% ee.[13,15] Interestingly, the configuration of the major enantiomer from this reaction is *R* instead of *S* obtained in the previous reaction (Scheme 1), indicating that the neighboring group participation was not operative in the xanthate reaction. Attempts to upgrade the enantiomeric excess of **5** by recrystallizing this crystalline compound from warm water were not successful. However, it was found that highly enantiomerically pure (*R*)-**5** could be obtained by carrying out the substitution reaction with 0.5 equiv. sodium carbonate and 2.5 equiv. of potassium xanthate to afford (*R*)-**5** in 84.6% ee and subsequently resolving this material with (*S*)-benzylmethylamine (Table 1, Entry 5). It was also found that it is important to obtain sufficiently pure (>84% ee) compound **5** prior to an efficient final resolution. Finally, deprotection of (*R*)-**5** with concentrated ammonium hydroxide in methanol afforded (*R*)-**4** in >96% ee and 90% yield. The optical purity of **4** was determined by derivatizing (*R*)-**4** with Ph_3COH/BF_3[16] to give (*R*)-**3**[12,13] and analyzing the latter by chiral HPLC. Following the strategy used for the preparation of (*R*)-**4**, (*S*)-2-mercaptosuccinic acid **4** was prepared in five steps from D-aspartic acid **1** in 50% overall yield and >96% ee.



Scheme 2.

Table 1
Preparation of 2-ethylxanthosuccinic acids **5** in water at 0–5°C

Entry[a]	Base	Equivalents[b]	Time	Yield (%)	%ee	Config.
1	K_2CO_3	1.0/1.0/1.0	92h	80.6	37.7	R
2	K_2CO_3	1.0/1.0/1.5	92h	73.4	56.2	R
3	Li_2CO_3	1.0/1.0/1.0	115h	100	28.8	R
4	Na_2CO_3	1.0/1.0/1.0	90h	100	70.6	R
5	Na_2CO_3	1.0/0.5/2.5	92h	100(67)[c]	84.6(96.2)[d]	R
6	Na_2CO_3	1.0/0.5/2.5	117h	100(63)[c]	85.6(96.1)[d]	S

[a](S)-**2** used except (R)-**2** used in entry 6; [b]Equivalents of **2**/base/potassium xanthate; [c]Yield in parentheses refers to the isolated yield of **5** after final resolution; [d]ee% in parentheses refers to the enantiomeric excess of **5** after final resolution, as determined by HPLC.[13]

In summary, a highly enantioselective method for the preparation of both (*R*)- and (*S*)-2-mercaptosuccinic acids, **4**, has been developed. This method is expected to be adaptable to the synthesis of other racemization prone 2-mercaptocarboxylic acids. In addition, the ready availability of both enantiomerically pure (*R*)- and (*S*)-**4** will make it possible to synthesize the above-mentioned, 2-mercaptosuccinic acid derived, biologically active compounds,[1–6] as well as others, in chiral nonracemic forms. Furthermore, considering the ease with which both (*R*)-/(*S*)-trithylmercaptosuccinic acids **3** and (*R*)-/(*S*)-ethylxanthosuccinic acids **5** were prepared and deprotected under mild acidic or basic conditions with high enantiomeric excesses, it is also expected that these intermediates, **3** and **5**, will become valuable chiral nonracemic, multifunctional sulfur-containing building blocks in asymmetric synthesis.

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12. Compound **3** has the following physical and spectroscopic properties: mp 190°C dec.; $[\alpha]_D$ +63.7 (*c* 1.13, MeOH) for (*R*)-**3** with 96.1% ee;[13] ^{1}H NMR (CD_3OD) δ 7.20–7.58 (m, 15H), 4.89 (bs, 2H), 3.22 (dd, J=3.7, 11.1 Hz, 1H), 2.41 (dd, J=11.1, 17.3 Hz, 1H), 1.42 (dd, J=17.3, 3.7 Hz, 1H).
13. The enantiomeric excesses of **3** and **5** were determined by chiral HPLC using a Chiralcel OJ-R column from Daicel Chemical Industries, Ltd.
14. For deprotection of tritylmercaptans, see: Pearson, D. A.; Blanchette, M.; Baker, M. L.; Guindon, C. A. *Tetrahedron Lett*. **1989**, *30*, 2739.
15. Compound **5** has the following physical and spectroscopic properties: mp 129–130°C; $[\alpha]_D$ +72.9 (*c* 1.43, MeOH) for (*R*)-**5** with 96.2% ee;[13] ^{1}H NMR (CD_3OD) δ 4.96 (bs, 2H), 4.68 (m, 2H), 2.75–3.1 (m, 3H), 1.42 (t, J=7.2 Hz, 3H).
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