Tetrahedron Letters,Vol.26,No.49,pp 6047-6050,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF ENANTIOMERICALLY PURE (S)-3-TRICHLOROMETHYLBUTYRIC ACID VIA ASYMMETRIC CONJUGATE ADDITION OF TRICHLOROMETHYL METAL COMPOUNDS TO A CHIRAL ENOATE. ACTIVATION EFFECT OF A SULFONYLAMINO GROUP[1]

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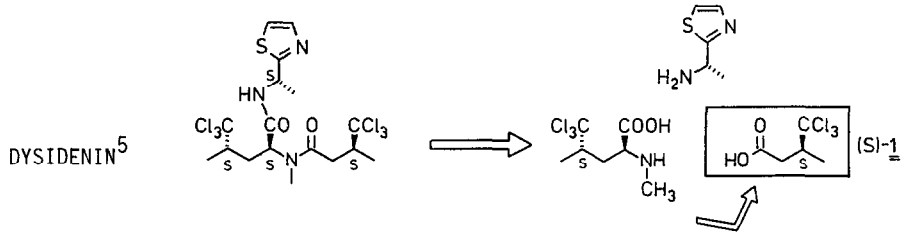
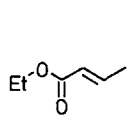
Summary: (+)(S)-3-Trichloromethylbutyric acid, a building block for syntheses of various marine natural products, can be prepared via 99:1 stereoselective conjugate addition of Cl_3CMgCl to the crotonate of a chiral auxiliary containing a sulfonylamino substituent.

Recently several polychlorinated metabolites derived from amino acid precursors have been isolated from the sponge Dysidea herbacea: dysidenin[3a], isodysidenin[3b], dysidin[3c], and related compounds[3d]. Common structural features suggested the use of (+)(S)-3-trichloromethylbutyric acid [(S)-1] as starting material for their synthesis[4], as is illustrated by the following retrosynthetic scheme for dysidenin:



Of many possible ways for preparation of (S)-1[4], asymmetric conjugate addition of a trichloromethyl metal compound to a chiral derivative of crotonic acid appeared to us particularly interesting for the following reasons: 1. Despite of numerous studies on the chemistry of halocarbenoids, conjugate additions of trihalomethyl anions have only been reported as side reactions (yield <12 %) of halocarben addition reactions[6]. 2. The trichloromethyl group can easily be reduced to the methyl group. This property allows convenient preparation of deuterated or tritiated compounds.

In the first phase of this project, concluded in 1983[7], >99 % enantiomerically pure (R)- and (S)-1 were prepared by application of the directed resolution method developed earlier in this laboratory[8]. We then directed our efforts to the conjugate addition reaction, first using $LiCCl_3$[9] (THF) as nucleophile. This very sensitive compound decomposes above -80 °C. Ethyl crotonate, first probed as electrophile, failed to react at this temperature. Considering that Lewis basic groups might facilitate the addition by coordination to the cation, we then choose the crotonic acid derivates 3 - 5 as acceptors. Of these, 3 did not react, 4 gave a variety of decomposition



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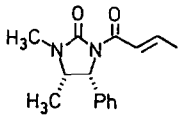

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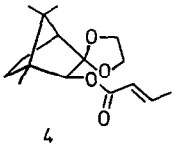

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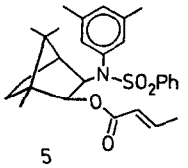

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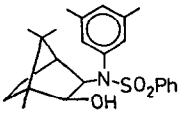

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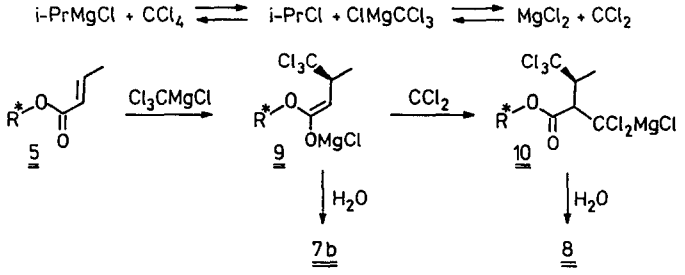
products; but the reaction of the ester 5[10] cleanly furnished crystalline products 7a,b in excellent yield (Table 1). However, the level of diastereoselectivity (7a:7b ≅ 60:40) was disappointingly low[11]. Variation of reaction conditions, limited in scope by the sensitivity of $LiCCl_3$, did not lead to improvement. But an interesting fact emerged: addition of $MgBr_2$ caused inversion of selectivity (7a:7b = 35:65, entry 4). Pursuing this lead, a suspension of Cl_3CMgCl in THF, prepared[12] by reacting CCl_4 with 1 equiv. of iPrMgCl at -110 °C, was used as reagent (Table 2). Again, 7b was obtained as predominant diastereomer, but with excellent diastereoselection (7a:7b = 1:99). However, a side product 8 was also formed to which we tentatively assign the (S)-configuration at C-3. Remarkably, only one out of four diastereomers of 8 could be detected (HPLC, MPLC, NMR) in the reaction mixture.

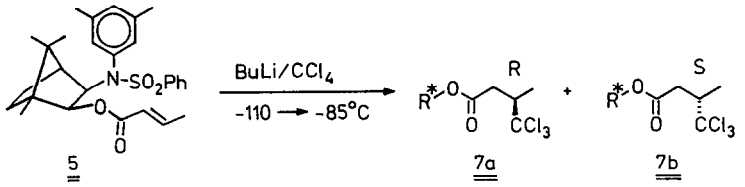
In order to increase the yield of the desired 7b to preparatively useful levels, it was necessary to suppress the formation of 8. This problem was solved on the basis of the following mechanistic rationale: Conjugate addition of Cl_3CMgCl to enoate 5 first yields the enolate 9. We ascribe the E-configuration to this compound because the observed[13] 3Si-face attack on 5 is most simply rationalized by assuming an antiplanar reactive conformation of the enoate group and approach of the nucleophile from the front, i.e. from the side not shielded by the bulky sulfonamide moiety[14]. Reaction of the enolate with CCl_2, formed by slow decomposition of Cl_3CMgCl[15], would give intermediate 10 from which 8 is produced by protonation.



5 9 10 7b 8

This rationale suggests that formation of 8 would be suppressed, if the carbene could be trapped. Of various ways investigated to achieve this, the most effective one was to apply the nucleophile iPrMgCl in excess. Thus, for preparation of the reagent a 3:1 instead of the usual 1:1 ratio of iPrMgCl and CCl_4 was applied. With this mixture the excellent result displayed by entry 4 of Table 2 was obtained. In contrast, addition of $CHCl_3$, supposed to react with iPrMgCl to give Cl_3CMgCl and thereby to remove the trapping agent, resulted in considerably increased formation of 8.

In conclusion, use of the conditions specified by entry 4 of Table 2 produced the desired isomer 7b with overall selectivity of 98:2. Two recrystallisations of the crude reaction product furnished pure 7b (HPLC) in 90 % yield. Saponification of this material (2 N KOH in methanol,r.t.)

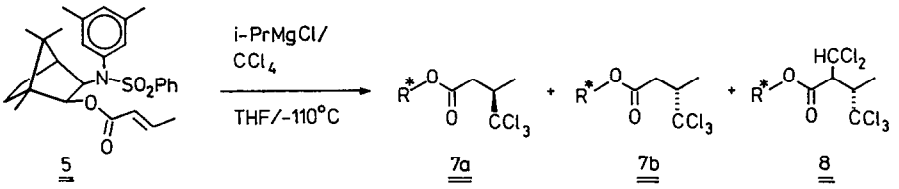


5 7a 7b

Table 1. Conjugate Addition of $LiCCl_3$[9] to the Enoate 5 (THF, molar ratio of $LiCCl_3$: 5 = 1.6).

Entry	Order of Addition	Additive	Diastereo-selectivity 7a : 7b	Yield [%]
1	normal [a]	-	62 : 38	85
2	inverse	-	59 : 41	94
3	inverse	$BF_3 \cdot Et_2O$ [b]	64 : 36	90
4	inverse	$MgBr_2 \cdot 2Et_2O$ [c]	35 : 65	53

[a] Normal: Isothermal addition of a solution of 5 to the suspension of $LiCCl_3$. [b] A solution of 5 and $BF_3 \cdot Et_2O$ (1.2 equiv) was added to the suspension of $LiCCl_3$ in THF. [c] Molar ratio of 5 : $MgBr_2 \cdot 2Et_2O$ = 1.



5 7a 7b 8

Table 2. Conjugate Addition of Cl_3CMgCl[12] to the Enoate 5 (THF, molar ratio of CCl_4 : 5 ≅ 15).

Entry	Order of Addition	Additive	Molar Ratio of iPrMgCl : CCl_4	Selectivity 7a : 7b : 8	Yield [%]
1	normal [a]	-	1 : 1	1 : 35 : 64	86
2	inverse	-	1 : 1	0.4 : 47.6 : 52	99
3	inverse	$CHCl_3$ [b]	1 : 1	1 : 20 : 79	99
4	inverse	-	2.7 : 1	1.2 : 98.1 : 0.7	99 ┐ 2 cryst.
				0 : 100 : 0	90 ┘

[a] Identical to [a] of table 1. [b] Molar ratio of $CHCl_3$: 5 = 6.

gave enantiomerically pure (+)(S)-3-trichloromethylbutyric acid in 95 % and recovered chiral auxiliary 6 in 96 % yield. Chiroptical and other data of the acid were in excellent agreement with those of the authentic sample[8].

1. This work was presented (G. H.) at "4. Vortragstagung der Arbeitsgemeinschaft Organische Chemie der Gesellschaft Deutscher Chemiker", Bad Nauheim (FRG), October 5, 1984.
2. New address: Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-6900 Heidelberg.
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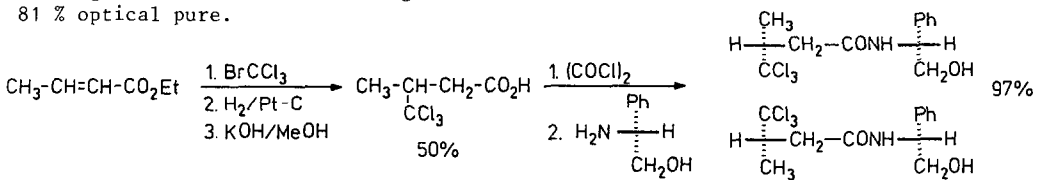
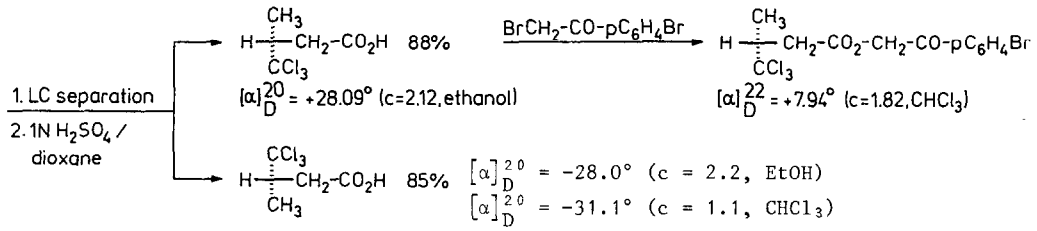
8. Racemic 3-trichloromethylbutyric acid was prepared via addition of $BrCCl_3$ to ethyl crotonate (R.L. Huang, J. Chem. Soc. 1956, 1749) in good yield. Conversion of the acid into diastereomeric amides of (-)(R)-α-phenylglycinol, separation by MPLC and amide cleavage was carried out according to our standard procedure [G. Helmchen, G. Nill, D. Flockerzi, M.S.K. Youssef, Angew. Chem. 91, 65 (1979), Angew. Chem. Int. Ed. Engl. 18, 63 (1979)]. Optical rotations of (+)- and (-)-1, and of their p-bromophenacyl derivatives are in excellent agreement with those given in ref. 4a. According to these values the acid described in ref. 4c was only 81 % optical pure.





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10. Ester 5 was prepared in 66 % yield by reaction of the chiral auxiliary 6 with crotonyl chloride (CCl_4, molecular sieve 4 Å, reflux). An alternative route via the chloroacetate of 6, phosphonate formation and Horner-Wittig reaction with acetaldehyde gave 5 in 65 % yield (E/Z ratio: 97:3).
11. Analyses of product mixtures and preparative separations were performed by HPLC and MPLC, respectively (silica gel, eluent: petroleum ether/ethyl acetate, 254 nm).
12. J.Villiéras, Bull. Soc. Chim. Fr. 1967, 1520.
13. Preferred 3Si-face attack is deduced from the known configurations of 7a and 7b.
14. This argument involves steric effects only. Considering the unique reactivity of enoate 5, however, it appears likely that coordination of the metal cation to the sulfonylamide group plays a role also. Alternative reaction modes, such as backside attack by Cl_3CMgCl bound to the sulfonyl group, can certainly not be excluded.
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(Received in Germany 12 September 1985)