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Synthetic Studies of Trichloroleucine Marine Natural Products. Michael Addition of $LiCCl_3$ to *N*-Crotonylcamphor Sultam

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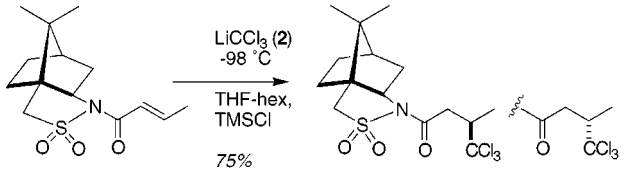
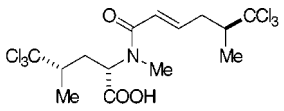
ABSTRACT



3 **4a** **4b**

Conjugate addition of trichloromethyllithium to *N*-crotonylcamphorsultam occurs in good yield at −98 °C in THF−hexanes. The formal incorporation of the "CCl_3^-" anion by 1,4-addition allows subsequent transformation to useful trichloromethyl-substituted intermediates.

Trichloroleucine natural products, such as (−)-herbacic acid (**1**),[1] are found in the marine sponges *Dysidea herbacea* and *Dysidea chlorea*[2] Both the L- or D-amino acids have been encountered.



1

Recent evidence suggests[1,3] that the CCl_3 groups of **1** may be derived by direct chlorination of leucine and parallel degradation of the resultant (2*S*,4*S*)-5,5,5-trichloroleucine to (*S*)-4,4,4-trichlorobutanoic acid (or its equivalent) and ketide homologation. To investigate this hypothesis we required a synthesis of **1** and a variety of putative non-chlorinated precursors by direct introduction of nucleophilic CCl_3^-. The CCl_3 group is easily dechlorinated and serves as a convenient surrogate for CH_3, CD_3, or CT_3 in labeling studies.

Conjugate additions of organometallic reagents to α,β-unsaturated carbonyl compounds are valuable C−C bond-forming reactions.[4] 1,4-Addition reactions of trichloro-

(1) MacMillan, J. B.; Molinski, T. F., *J. Nat. Prod.*, in press.

(2) Fu, X.; Ferreira, M. L. G.; Schmitz, F. J.; Kelly-Borges, M. *J. Nat. Prod.* **1998**, *61*, 1226−1231.

(3) (a) Sitachitta, N.; Rossi, J.; Roberts, M. A.; Gerwick, W. H.; Fletcher, M. D.; Willis, C. L. *J. Am. Chem. Soc.* **1998**, *120*, 7131−7132. (b) Hartung, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1209−1211.

(4) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992; p 373.

(5) (a) 2-Cyclohexenone with **2** and Al(2,6-di-$PhC_6H_3O)_3$: 1,4-adduct, 60%; Maruoka, K.; Shimada, I.; Imoto, H.; Yamamoto, H. *Synlett* **1994**, 519−520. (b) 2-Cyclopentenone with **2**: 1,4-adduct (23%) accompanied by 1,2-adduct (34%); Krebs, J.; Weber, A.; Neuenschwander, M. *Chimia* **1981**, *35*(2), 55−57. **2** with enoylphosphoranes, 80−90%, (c) Cooke, M. P., Jr.; Jaw, J.-Y. *J. Org. Chem.* **1993**, *58*, 267−269. Addition of stablilized CCl_3^- generated in other ways to Michael acceptors are also reported. The yields, with one exception, are poor due to strong competition from dichlorocyclopropanation. Phase-transfer catalytic generation of CCl_3^- and addition to crotonates, 3−19%: (d) Dehmlow, E. V.; WIlkenloh, J. *Chem. Ber.* **1990**, *123*, 583−587. (e) Dehmlow, E. V. *Liebigs Ann. Chem.* **1972**, *758*, 148−154. Addition to acrylate ester, acrylonitrile, vinyl sulfone, ca. 10%: (f) Nerdel, F.; Brodowski, W.; Buddras, J.; Fligge, M.; Weyerstahl, P.; Ulm, K.; Finger, C.; Klamann, D. *Chem. Ber.* **1968**, *101*, 1407−1413. Addition to menthyloxy 2(5*H*)-furanone, 14% ((g) Kang, F.-A.; Yu, Z.-Q.; Yin, H.-Y.; Yin, C.-L. *Tetrahedron: Asymmetry* **1997**, *8*, 3591−3596) and electrochemical base-generated CCl_3^- with acrylates, acryonitriles, 18−87% ((h) Shono, T.; Ishifune, M.; Ishige, O.; Uyama, H.; Kashimura, S. *Tetrahedron Lett.* **1990**, *49*, 7181−7184).

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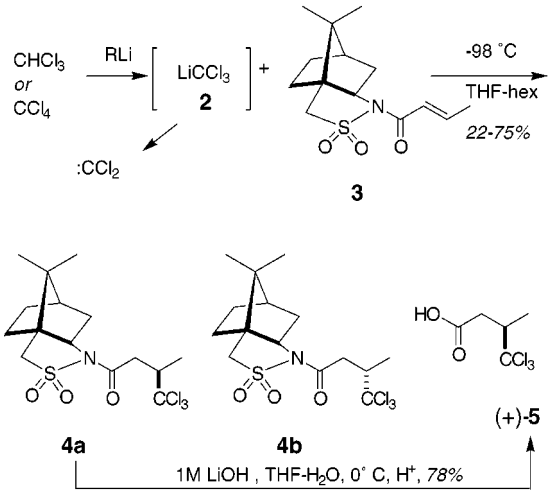
methyllithium ($LiCCl_3$, **2**) or other equivalents of the CCl_3^- anion to enones, enoates, and acrylonitriles have been reported, but yields are generally low.[5]

The reason lies partly in the low stability of **2** which rapidly undergoes α-elimination of LiCl to give electrophilic dichlorocarbene above ~−80 °C.[6] No examples of additions of **2** to enoyl amides or enoyl sulfonamides are known. We conjectured that the relatively "soft" nucleophile **2** might favor conjugate addition to less-reactive Michael acceptors at low temperatures and were delighted to find that this was, indeed, the case. We now describe that conjugate addition of **2** to an enoyl sulfonamide, (1*S*)-*N*-crotonyl-2,10-camphor sultam (−)-**3**, occurs in good yield in the presence of TMSCl.

Initial attempts to induce 1,4-addition of **2** to (−)-**3**[7] (Scheme 1) were met with partial success. Generation of **2**

Scheme 1



by addition of a slight excess of *n*-BuLi to $CHCl_3$ in THF at −78 °C in the presence of (−)-**3** gave only starting material and a complex mixture of products. When the reaction was repeated at −98 °C, the epimeric conjugate addition products **4a** and **4b** (62:38) were obtained in 27% yield after chromatography (Table 1, entry 1). Separation of the major

Table 1. Conjugate Additions of $LiCCl_3$ to (−)-**3**[a]

entry	$CHCl_3$, equiv	*n*-BuLi, equiv	additive (1.0 equiv)	total yield **4a** + **4b**, %	**4a**:**4b**
1[b]	1.2	1.1		27%	62:38
2[b]	1.2	1.1[e]	$MgCl_2$	20%	70:30
3[c]	5.0	5.0		< 5%	
4	5.0	5.0		22%	55:45
5	5.0	5.0	$ZnCl_2$	NR	
6	20.0	20.0		25%	
7	5.0	5.0	TMSCl	75% (87%)[d]	55:45
8	5.0	5.0	$TiCl_4$−TMSCl	NR	

[a] $CHCl_3$ was added to *n*-BuLi or *sec*-BuLi in THF at −98 °C. [b] Generation of **2** in the presence of (−)-**3**. [c] Inverse addition of $CHCl_3$ and *n*-BuLi. [d] 87% based on consumed starting material. [e] *sec*-BuLi.

isomer **4a** from **4b** was achieved by repeated fractional crystallization from *n*-hexane—the less soluble isomer (−)-**4a** was obtained as colorless crystals, mp 134−5 °C, $[\alpha]_D$ −41.0° ($CHCl_3$).[8]

The assignment of configuration of the newly created stereogenic center followed from saponification of (−)-**4a** (LiOH, aqueous THF) and conversion to the known acid (+)-**5** (78%).[9] Diastereoselectivity increased slightly (70:30 dr,[10] entry 2) with 1.1 equiv of *sec*-BuLi in the presence of $MgCl_2$ (1.0 equiv), although the yield was still low (20%). A dramatic improvement in yield of **4a**:**4b** was obtained with use of excess **2** (5 equiv, entry 7) and addition of TMSCl (75% yield, 87% based on consumed sm (55:45 dr).

TMSCl appears to activate (−)-**3** toward conjugate addition,[11] but the presence of transition metals ($TiCl_4$, $ZnCl_2$) gave no reaction, possibly due to catalytic decomposition of **2** to CCl_2.[6a]

The relatively "soft" trichloromethyllithium appears to be well suited for conjugate addition to enoyl sulfonamides. Activation of (−)-**3** with TMSCl toward conjugate addition supports a nucleophilic mechanism, in contrast to earlier claims that $LiCCl_3$ is electrophilic.[6b]

The CCl_3 group is relatively robust and tolerates further reaction (Scheme 2). Esterification of (±)-**5** (MeOH, catalytic

(6) Köbrich, G. *Angew. Chem., Int. Ed.* **1972**, *11*, 473−485 and references therein. (b) Miller, W. T., Jr.; Whalen, D. M. *J. Am. Chem. Soc.* **1964**, *86*, 2089−2091.

(7) Prepared by *N*-acylation of (−)-(1*S*)-camphor-2,10-sultam with crotonyl chloride (NaH, toluene, 0−25 °C, 70%): see *ent*-**3**, Vandewalle, M.; van der Eycken, J.; Oppolzer, W.; Vulliod, C. *Tetrahedron* **1986**, *42*, 4035−4043.

(8) $CHCl_3$ (248 mg, 2.08 mmol, 5 equiv) was added to a mixture of 0.5 mL of THF and *n*-BuLi (2.13 M in hexanes, 2.00 mmol, 5 equiv) at −98 °C, without allowing the temperature to rise above −80 °C. A solution of **3** (0.1140 g 0.40 mmol, 1 equiv) in THF (1.0 mL) was introduced, slowly, followed by TMSCl (0.223 mg, 2.05 mmol) after 50 min. The temperature was raised to −78 °C and the mixture quenched with aqueous NH_4Cl after a further 90 min. Workup (ether) and silica chromatography (1:9 *n*-hexane/CH_2Cl_2) gave **4a**:**4b** (75%, 87% based on consumed starting material). Six crystallizations from *n*-hexane gave pure **4a**: $C_{15}H_{22}Cl_3NO_3S$; mp 134−135 °C; $[\alpha]_D$ −41.0° (c = 1.14, $CHCl_3$); IR (NaCl) ν 1693 cm^{-1}; ^1H NMR (C_6D_6) δ 3.77 (dd, 1H, J = 16.4, 1.8 Hz), 3.50 (m, 2H), 3.29 (dd, 1H, J = 16.4, 9.7 Hz), 2.74, 2.72 (ABq, 2H, J = 13.8 Hz), 2.00 (ddd, 1H, J = 12.0, 8, 0, 3.6 Hz), 1.87 (dd, 1H, J = 14.0, 8.0 Hz), 1.30 (bd, 3H, J = 6.5 Hz), 1.28 (m, 2H), 1.10 (m, 1H), 1.01 (s, 3H), 0.75 (m, 1H), 0.57 (ddd, 1H, J = 12.0, 9.4, 3.1 Hz), 0.41, (s, 3H); ^{13}C NMR (C_6D_6) δ 169.5 (C=O), 105.6 (CCl_3), 65.7 (d), 52.9 (t), 52.4 (d), 48.7 (s), 48.0 (s), 45.3 (d), 40.2 (t), 39.2 (t), 32.9 (t), 26.8 (t), 21.4 (q), 20.0 (q), 17.4 (q); HREIMS, found m/z 401.0357 (M^+); $C_{15}H_{22}Cl_3NO_3S$ requires 401.0386. Compounds **4a**:**4b** were separable by HPLC (Dynamax silica, 10 × 250 mm, 3 mL/min, 1:4 EA/hexane). ds was monitored by integration of ^1H NMR (300 MHz, C_6D_6) *gem* dimethyl signals of **4a** (δ 0.42, s 3H; 1.01, s, 3H) and **4b** (δ 0.39, s, 3H; 0.96, s, 3H).

(9) De Laszlo, S. E.; Willard, P. G. *J. Am. Chem. Soc.* **1985**, *107*, 199−203. We also prepared (±)-**5** by the method described above (free-radical conjugate addition of $BrCCl_3$ to crotonic acid, Zn reduction) and resolved (+)-**5** and (−)-**5** by repeated recrystallization of the corresponding (−)-cinchonidine salts (aqueous MeOH).

(10) This is consistent with addition of **2** to the metal-chelate-preorganized *s-cis* conformation of **3**: cf. Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **1989**, *45*, 479−488.

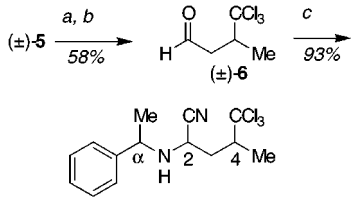
(11) TMSCl is well known to accelerate conjugate addition of cuprates to enones and enoyl derivatives, e.g., Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *J. Organomet. Chem.* **1987**, *334*, 255−261 and other citations in ref 4.

(12) Inaba, T.; Fujita, M.; Ogura, K. *J. Org. Chem.* **1991**, *56*, 1274−1279.

(13) The configuration of **7a** was verified on the basis of Inaba's work[12] and comparative spectroscopic analysis.

(14) (a) Lee, G. M.; Molinski, T. F. *Tetrahedron Lett.* **1992**, *33*, 7671−7674. (b) Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett.* **1978**, 4945−4948.

Scheme 2



	α, C2, C4	ratio
7a	*R, R, S*	44
7b	*R, R, R*	25
7c	*R, S, S*	17
7d	*R, S, R*	14

[a] MeOH, H_2SO_4, Δ. [b] DIBAL, −78 °C, toluene. [c] (*R*)-α-Methylbenzylamine, KCN, H_2O, MeOH, $NaHSO_3$, 0−25 °C.

H_2SO_4, reflux) followed by reduction (DIBAL, −78 °C, toluene) gave aldehyde (±)-**6**[9] (58%, two steps). Application of Inaba's modified Strecker synthesis[12] with (±)-**6** and (*R*)-α-methylbenzylamine (KCN, $NaHSO_3$, aqueous MeOH) gave a 93% yield of optically active aminonitriles **7a**−**d** which were separated by HPLC (isolated ratios 44:25:17:14, respectively) to provide the major isomer **7a** in ∼40% yield.[13] From the isolated ratios of **7a**−**d**, we conclude that diastereoselectivity, with respect to generation of the new stereogenic center C-2, is ∼1−1.7 to 1:2.6 and is significantly influenced by the bulky CCl_3 group at C-4.

We and others[14] have shown that the CCl_3 group in trichloroleucine natural products can be dechlorinated easily to either a CH_3 group (Zn, AcOH) or a CD_3 group (Zn, AcOD). Thus, the formal 1,4-addition of "CCl_3^- anion" provides a convenient and inexpensive alternative to 1,4-addition of d_3-Me Grignard reagents for synthesis of trideuteriomethyl-labeled compounds that are useful for isotopic labeling studies in trichloroleucine biosynthesis. Progress in this area in the latter and synthesis of (−)-**1** will be reported in due course.

Acknowledgment. This work was funded in part by the California Sea Grant College Program (R/MP-57A) and office of research, UC Davis.

Supporting Information Available: Preparation, characterization, and configurational assignments of **7a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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