Scope and Mechanism of Deprotection of Carboxylic Esters by Bis(tributyltin) Oxide[1]

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Received February 25, 1994 (Revised Manuscript Received September 26, 1994®)

Methyl and ethyl esters of aliphatic and aromatic carboxylic acids as well as benzyl carboxylates, thiol esters and double esters such as (pivaloyloxy)methyl carboxylates have been successfully cleaved with bis(tributyltin) oxide to give the free carboxylic acids in good yields. The reaction is carried out in aprotic solvents under essentially neutral conditions and thus this method can serve as an ideal procedure for the cleavages of esters with other functional groups and/or protecting groups acid and/or base sensitive. We demonstrated that the reaction displays a high level of chemoselectivity between methyl and ethyl esters versus *tert*-butyl esters and γ-lactones. Bis(tributyltin) oxide is also a highly efficient reagent for the cleavage of acetates of primary and secondary alcohols and phenols. The limitations we found in the use of this reagent include the lack of cleavage of esters sterically hindered around the carboxyl carbon and the carbinol group (i.e., esters of tertiary alcohols) and in carboxylic esters that contain a fluoroalkyl substituent. A resonable mechanistic explanation is discussed to account for the reaction pathway of the acyl-oxygen cleavage of (−)-(1*R*)-menthyl acetate.

Introduction

Developing efficient and mild methods for the selective cleavage of carboxylic esters to afford the carboxylic acids continues to be a significant aspect of experimental organic chemistry. We recently[2,3] have developed a simple and effective, non-hydrolytic method for the cleavage of simple carboxylic esters, such as methyl, ethyl, phenacyl, and phenyl esters, as well as for the deprotection of double esters, such as (pivaloyloxy)methyl esters, by the action of bis(tributyltin) oxide[1] (henceforth abbreviated BBTO).

Since a carboxylic ester possesses a hard center (carboxyl carbon) and a soft center (carbinol carbon), using the principles of hard/soft acid base theory,[4,5] hard nucleophiles are predicted to show a preference for attack on the carboxy carbon (hard–hard interaction) rather than the carbinol carbon (hard–soft interaction) (Figure 1). In evaluating the various hard nucleophiles which are available, "naked" fluoride anion[6] is one choice. Similarly, pertinent internal bifunctional systems consisting of a hard acid and a hard nucleophile should attack the carboxylic ester at the carboxy center rather than at the carbinol center and, therefore, accomplish acyl-oxygen cleavage without affecting the stereochemistry of a chiral center at the carbinol carbon.

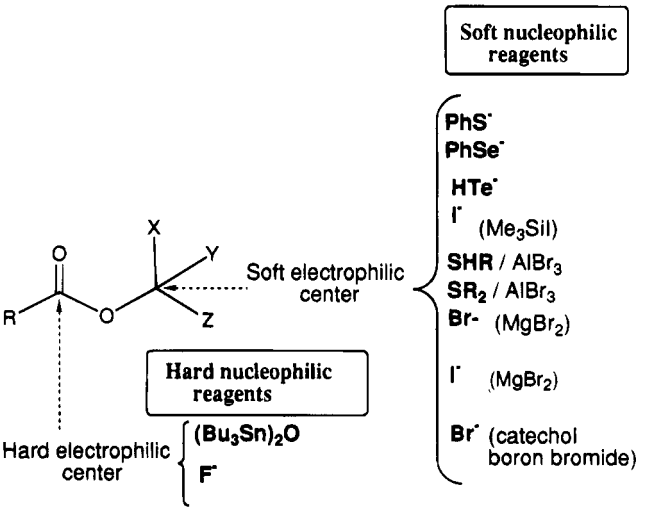


Figure 1.

On the other hand, the alternative approach of cleaving esters via nucleophilic attack at the carbinol carbon under non-hydrolytic conditions in non-hydroxylic solvents can be employed. Thiophenoxide, alkanethiolate, trithio-carbonate, ethanedithiolate, sulfide, phenyl selenide, hydrogen selenide, and telluride anions are representative of the soft nuclephile class. Besides, the most widely used combination systems, consisting of a hard acid and a soft nucleophile, are: trimethylsilyl iodide, aluminium halide-ethanethiol, aluminium halide-dialkyl sulfide, aluminium triiodide, magnesium bromide, magnesium iodide, and catechol boron bromide. In a recent review[7] we provided an update on methods for

® Abstract published in *Advance ACS Abstracts,* November 1, 1994.

(1) The naming of organotin compounds follows the trivial system by using "tin" as a suffix, as in: Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987; p 3.

(2) Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1988**, *29*, 6893.

(3) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1991**, *32*, 4239.

(4) (a) Pearson, R. G. *J. Am. Chem Soc.* **1963**, *85*, 3533. (b) Hudson, R. F. *Coordination Chemistry Reviews* **1966**, 89. (c) Saville, B. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 928. (d) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827. (e) Pearson, R. G.; Songstad, J. *J. Org. Chem.* **1967**, *32*, 2899. (f) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512. (g) Pearson R. G. *J. Am. Chem. Soc.* **1988**, *110*, 7684. (h) Pearson, R. G. *J. Org. Chem.* **1989**, *54*, 1423. (i) Pearson, R. G. *Acc. Chem. Res.* **1993**, *26*, 250.

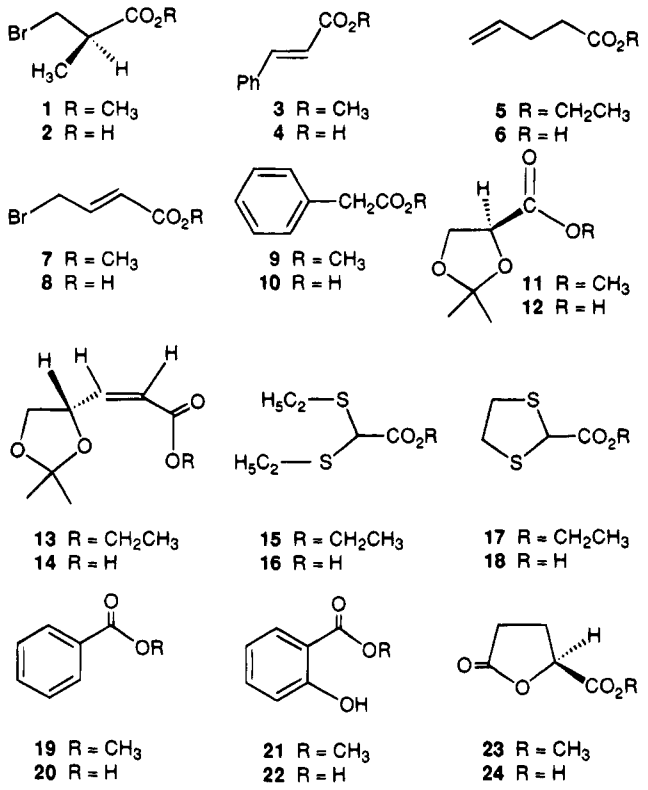
(5) For a review see: (a) Pearson, R. G. *Hard and Soft Acids and Bases*; Dowden, Hutchinson, & Ross Inc.: Stroudsberg, 1973. (b) Ho, T. L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977. (c) Ho, T. L. *Chem. Rev.* **1975**, *75*, 1.

(6) The only unsolvated ("naked") fluoride anions that have proven reliable are tetramethylammonium fluoride, phosphazenium fluoride, and *N,N,N*-trimethyl-1-adamantylammonium fluoride, see: (a) Mascaretti, O. A. *Aldrichimica Acta* **1993**, *26*, 47. (b) Harmon, K. M.; Southworth, B. A.; Wilson, K. E.; Keefer, P. K. *J. Org. Chem.* **1993**, *58*, 7294.

(7) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron* **1993**, *49*, 3691.

0022-3263/94/1959-7259$04.50/0

Chart 1



chemical deprotection of carboxylic esters. One cannot expect a single reagent to fullfill all the requirements for the cleavage of esters of different kinds. Currently a wide range of other non-hydrolytic methods are also available; among which hydrogenolysis, catalytic transfer hydrogenation, and nucleophilic substitution of allylic systems activated with Pd°, are the most widely used.[7]

Whatever strategy is chosen for the nucleophilic cleavage of carboxylic esters, the mechanistic implications have to be considered along with the steric hindrance around the carbinol and carboxy carbons and the chemical properties and drawbacks of each reagent. In 1988[2] and 1991[3] we reported preliminary details of our studies on the applicability of BBTO, a combination of a hard acid and a hard nucleophile, for the cleavage of a variety of carboxylic esters. In this paper we provide additional insight into (a) the selectivity of BBTO in the presence of a variety of functional groups, and (b) the scope and limitations of this method relative to other ester acyl–oxygen and alkyl–oxygen cleavage processes in the literature.

Results and Discussion

I. Cleavage of Simple Alkyl Esters. To test the generality of the procedure for the cleavage of primary alkyl carboxylic esters, we have carried out the reaction on a variety of methyl and ethyl esters of aliphatic and aromatic carboxylic acids containing representative functional groups (Chart 1). The results are summarized in Table 1. Note that the procedure seems to be generally applicable for the conversion of primary alkyl carboxylic esters into carboxylic acids in good yields and the reagent BBTO is tolerant of a large range of functional groups including lactones, alkenes, cyclic ketals, acyclic and cyclic dithioketals, and vinyl bromides.

It is particularly noteworthy that treatment of methyl (*S*)-(+)-5-oxo-tetrahydro-2-furoate (**23**) with BBTO in acetonitrile at 60 °C for 24 h led to the (*S*)-(+)-5-oxo-tetrahydro-2-furoic acid (**24**). A similar chemoselectivity was reported by Yamamoto and co-workers for the hydrolysis of methyl (*R*)-5-oxo-tetrahydro-2,3 dimethyl-2-furoate with lithium hydroxide.[8] The optical purities of acids **2**, **12**, and **24** were completely retained. An advantage of the BBTO-induced cleavage of esters over the traditional saponification is that the ester is not exposed to strong base.

Table 1. Selected Methyl and Ethyl Carboxylic Esters

entry	starting ester	product[a]	condns[b]	yield[c] (%)
1	**1**	**2**	toluene, reflux, 48 h	60
2	**3**	**4**	benzene, 80 °C, 24 h	90
3	**5**	**6**	toluene, reflux, 48 h	42
4	**7**	**8**	toluene, 80 °C, 10 h	70
5	**9**	**10**	benzene, 80 °C, 13 h	95
6	**11**	**12**	toluene, 80 °C, 10 h	48
7	**13**	**14**	toluene, 80 °C, 10 h	70
8	**15**	**16**	toluene, 80 °C, 10 h	52
9	**17**	**18**	toluene, 80 °C, 10 h	52
10	**19**	**20**	toluene, 80 °C, 10 h	80
11	**21**	**22**	benzene, 80 °C, 24 h	85
12	**23**	**24**	acetonitrile, 60 °C, 24 h	55

[a] All products gave satisfactory ^1H and ^{13}C NMR spectral data. [b] See the Experimental Section for procedures. [c] Yields are based on pure isolated material.

Methyl and ethyl esters are commonly encountered in organic synthesis because the particular advantage of these types of esters lies in their simple and easy preparation.[9] Recently, methyl and ethyl as well as other alkyl carboxylates have been prepared in good to excellent yields by reaction of tributyltin carboxylates, obtained by heating an equimolecular mixture of carboxylic acid and BBTO in refluxing benzene, with alkyl halides in the presence of CsF.[10] The significance of the synthetic versatility of BBTO lies in the fact that it is possible to mask carboxylic acids temporarily as methyl or ethyl esters in the course of a multistep synthesis of polyfunctional molecules and then selectively deprotect these esters in the presence of diverse functional groups under mild conditions. Another aspect of this method is that the reaction is carried out under essentially neutral conditions and thus can serve as an ideal procedure for the cleavage of esters of acid and/or base sensitive compounds.

II. Cleavage of Sterically Hindered Esters around the Carboxyl Carbon and Carbinol Carbon. In the present study, we have examined the viability of the BBTO cleavage reaction with sterically hindered methyl esters around the carboxyl carbon. Also, to achieve an understanding of the effects of steric hindrance on the carboxyl versus the alcohol; we selected acetates of primary, secondary and tertiary alcohols (Chart 2). Examination of Table 2 shows that BBTO did not cleave the methyl esters of pivalic acid (**25**), O-methylpodocarpic acid (**27**) and 1-adamantanecarboxylic acid (**28**). Furthermore, when methyl 1-adamantaneacetate (**30**) was treated with BBTO under similar conditions, the reaction was not complete, giving only 25% of 1-adamantaneacetic acid (**31**). By contrast, the phenylselenide induced cleavage at the carbinol center of the hindered methyl esters

(8) Yamamoto, Y.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Org. Chem.* **1986**, *51*, 886.
(9) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; J. Wiley & Sons: New York, 1991.
(10) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1992**, *57*, 2166

Chart 2

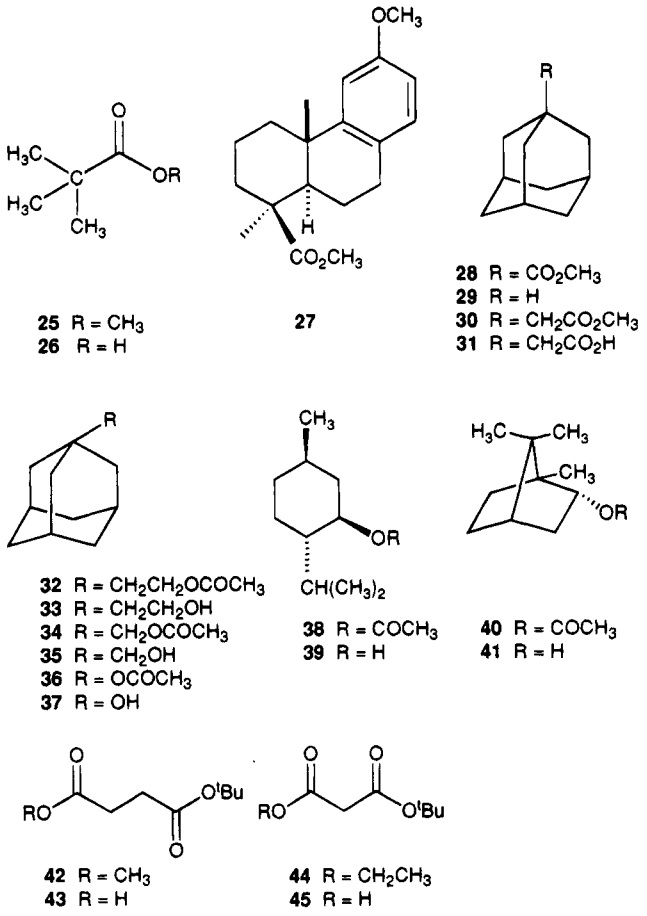


Table 2. Methyl Carboxylic Esters Sterically Hindered around the Carboxyl Carbon

entry	starting ester	product	condns[b]	yield[a] (%)
13	**25**	**26**	B	5
14	**27**	no reaction	toluene/DMF, 80 °C, 96 h	
15	**28**	**29**	B	10
16	**30**	**31**	B	25

[a] Isolated yields. [b] B: toluene, reflux, 72 h.

Table 3. Acetates of Primary, Secondary, and Tertiary Alcohols

entry	starting ester	product	condns[b]	yield[a] (%)
17	**32**	**33**	E	97
18	**34**	**35**	E	97
19	**36**	**37**	E	15
20	**38**	**39**	toluene, 110 °C, 24 h	70
21	**40**	**41**	E	13

[a] Isolated yields. [b] E: acetonitrile, 90 °C, 96 h.

25 and **27** afforded the corresponding carboxylic acids in excellent yields.[11]

The results in Table 3 indicate that the cleavage of acetate of primary alcohol **32** and primary neopentyl **34** were accomplished almost quantitatively. Whereas, when this reaction was used to cleave the tertiary 1-adamantyl acetate (**36**), the yield was considerably lower (15%) than that obtained from 1-adamantylethyl and adamantylmethyl acetates. A comparison of the results obtained with acetates of secondary alcohols **38** and **40** also reveals the role of the steric hindrance.

(11) Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605.

Table 4. Selective Cleavage of Methyl and Ethyl Esters in the Presence of *tert*-Butyl Esters

entry	starting ester	product	condns	yield[a] (%)
22	**42**	**43**	toluene, 80 °C, 24 h	70
23	**44**	**45**	toluene, 104 °C, 3 h	47

[a] Isolated yields.

A comparison of the results obtained in Tables 2 and 3 reveals the difference in reactivity of **30** compared with **34** and leads to the conclusion that steric hindrance at the carboxyl inhibits the reaction more than steric at the carbinol center.

It was apparent that this difference in reactivity could be exploited for the chemoselective deprotection of primary alkyl esters in the presence of tertiary alkyl esters. The results of this strategy are summarized in Table 4.

The chemoselectivity of BBTO towards carboxylic diesters was found to be excellent. The reagent selectively cleaved the methyl ester of *tert*-butyl methyl succinate (**42**) and the ethyl ester of *tert*-butyl ethyl malonate (**44**), in the presence of the *tert*-butyl ester group in 70% and 47%[12] isolated yield. None of the methyl succinate half ester or succinic acid and ethyl malonate half ester or malonic acid was seen within the limits of detection by ^{1}H NMR (<3%). Thus, the BBTO approach provides a useful alternative to the chemical saponification that often results in statistical mixtures. This finding that methyl and ethyl esters could be cleaved selectively by BBTO in the presence of *tert*-butyl esters complements the catechol boron bromide[13] selective cleavage of *tert*-butyl esters in the presence of methyl and ethyl esters. Jung and Lyster have reported[14] that *tert*-butyl and benzyl ester were rapidly dealkylated at 25 °C by trimethylsilyl iodide, whereas methyl, ethyl and isopropyl ester require higher reaction temperatures. These results indicate that the reagent allows selectivity between these esters.

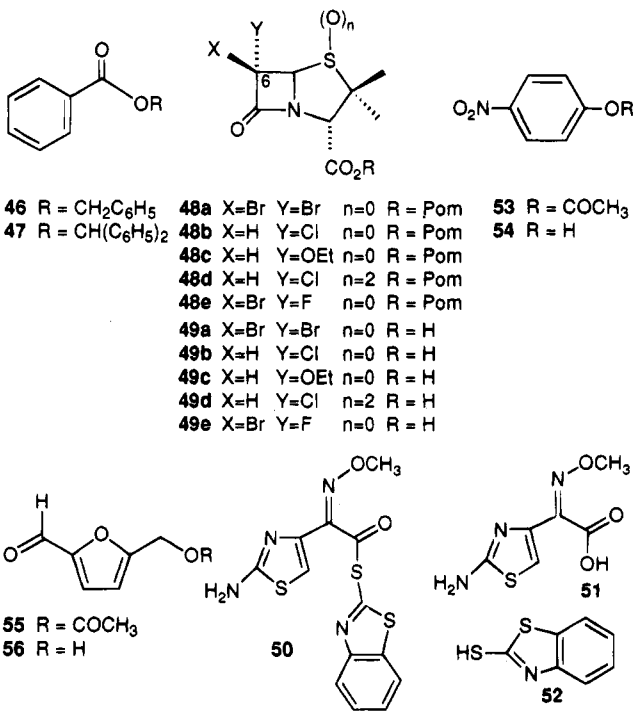
III. Cleavage of Benzyl, Benzhydryl, (Pivaloyloxy)methyl Carboxylate, and Thiol Esters. Benzyl, benzhydryl, (pivaloyloxy)methyl carboxylate and thiol esters are likewise cleaved on treatment with BBTO (Chart 3). Table 5 summarizes the results for the reaction of BBTO with these esters under various conditions.

Benzyl benzoate (**46**) is cleaved at 80 °C within 48 h to give benzoic acid (**20**) in 70% yield, whereas benzhydryl benzoate (**47**), in contrast, required 120 h at 90 °C and even under these conditions the reaction was not complete and only 48% of **20** was obtained. This experimental result indicates that the benzhydryl ester group, another important protecting group, cannot be easily deblocked by the present method.

Initially our interest in BBTO arose in connection with development of an assay for β-lactamase inhibitory activity. We required a method for deprotection of (pivaloyloxy)methyl (Pom) 6-halo- and 6,6-dihalopenicillanate esters to liberate the 6-halo- and 6,6-dihalopenicillanic acid. The classic saponification and acidic methods were not applicable since they brought about the destruction of the β-lactam ring. Sodium thiophenox-

(12) The low yield is probably caused by the formation of emulsions during the work-up which makes extractions difficult.
(13) Boeckman, R.; Potenza, J. *Tetrahedron Lett.* **1985**, *26*, 1411.
(14) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968.

Chart 3



ide,[15] a soft nucleophile, non-basic reagent was inadequate since this reagent in the 6-halo- and 6,6-dihalopenicillanate series might lead to substitution at carbon 6. We found that trimethylsilyl iodide did not cleave Pom penicillanate derivatives, and with boron tribromide the results were not reproducible. Then, our search was directed to BBTO; we found that this reagent allows the selective cleavage of the (pivaloyloxy)methyl penicillanate esters of compounds **48a-d** in the presence of the other functional groups of the azetidinone and thiazolidine rings and their substituents. However, attempts to effect cleavage of Pom 6β-bromo-6α-fluoropenicillanate (**48e**) resulted in the destruction of the β-lactam moiety. This result may be due to a fluorodestannylation reaction.[16] It is well known that the hard tin atom has a great tendency to interact with the hard fluorine atom.[17] In the case of compound **48e** hydrolysis with pig liver esterase (PLE) afforded the desired 6β-bromo-6α-fluoropenicillanic acid. This example demonstrates a limitation associated with the BBTO methodology.

It is interesting to note that BBTO is effective for the liberation of the carboxy and the thiol functions of thioesters. Thus, treatment of 2-mercaptobenzothiazolyl (-2-aminothiazol-4-yl)-2-methoxyiminothioacetate (**50**) with BBTO in acetonitrile at 80 °C for 2 h afforded the corresponding (2-aminothiazol-4-yl)-2-(methoxyimino)-acetic acid (**51**) and 2-mercaptobenzothiazole (**52**) in 57% yield. One method used to prepare thiol esters is the reaction of tri(butyltin)mercaptide with acyl chlorides.[18]

IV. Cleavage of Esters with Recovery of the Alcohols. The formation of carboxylic esters, particularly acetates, is a useful and widely employed method for protection of the alcohol functional group.[9] It has played a major role in carbohydrate and nucleoside protecting group chemistry. BBTO and tri(butyltin)-methoxide have been utilized in carbohydrate chemistry for the regioselective O-deacetylation of anomeric primary and secondary acetates to give products with free hydroxyl groups.[19]

The cleavage of acetate esters of representative primary, secondary and tertiary alcohols and phenolic hydroxyl groups are summarized in Tables 3 and 6. The reaction proceeds in a straightforward manner as described in the Experimental Section, i.e., after addition of BBTO a solution of the acetate ester in toluene was heated under reflux; once TLC indicated that the reaction had reached completion, chromatography and work-up afforded the alcohols in good yields.

Studies on ester of chiral alcohol **38** showed that BBTO promotes regioselective cleavage at the acyl–oxygen bond. Thus, (1*R*,2*S*,5*R*)-(−)-menthyl acetate (**38**) affords exclusively (1*R*,2*S*,5*R*)-(−)-menthol (**39**), which represents a simple method for the deprotection of chiral alcohols with complete retention of configuration.

4-Nitrophenyl acetate (**53**) was deprotected with BBTO in benzene at room temperature. Acetic acid and 4-nitrophenol (**54**) were recovered in excellent yield from the organic phase by extraction with 5% aqueous sodium hydrogen carbonate and 10% aqueous sodium hydroxide, respectively. Deprotection of the phenolic hydroxyl group was complete in less than 1.5 h in the presence of the nitro group.

Similarly, 5-(hydroxymethyl)-2-furaldehyde (**56**) was obtained from 5-(acetoxymethyl)-2-furaldehyde (**55**) in excellent yield. This example also demonstrates the good compatibility with the aldehyde group.

V. Purification. One of the practical difficulties encountered in developing the new reagent was the removal of excess of BBTO and organotin side products after the reaction. The moderate yields obtained for the reaction of compounds **5**, **11**, **15**, **17**, and **23** was due to the loss of material during workup.

Most of these organotin compounds are highly soluble in nonpolar solvents and very insoluble in water. We have used these properties extensively to purify carboxylic acids and overcome the problem. Normally, carboxylate salts are cleanly extracted into an aqueous phase, while the tin derivatives remain in the organic phase. We have also made extensive use of the procedure developed by Berge and Roberts.[20] Their method is based on the very high solubility of organotin derivatives in hexane and the preferential partitioning of other organic molecules into acetonitrile in the acetonitrile-hexane two phase system. We have also found that filtration through a short pad of C-18 reverse-phase silica gel and elution with mixtures of acetonitrile–water is one of the most useful ways to remove organotin derivatives. Recently, Farina[21] reported a simple procedure for separation of organotin derivatives by column chromatography using reverse-phase silica gel; however, its application in preparative work is hampered by the high cost of the C-18 silica gel.

VI. Mechanism. In conformity with the stereochemical result obtained in the cleavage at the acyl–oxygen bond of (1*R*,2*S*,5*R*)-(−)-menthyl acetate (**38**), yielding

(15) (a) Sheehan, J. C.; Daves, G. D. *J. Org. Chem.* **1964**, *29*, 2006. (b) Bamberg, P.; Ekström, B.; Sjoberg, B. *Acta Chim. Scand.* **1967**, *21*, 2210.
(16) Harp, D. N.; Gingras, M. *Tetrahedron Lett.* **1987**, *28*, 4373.
(17) Harp, D. N.; Gingras, M. *J. Am. Chem. Soc.* **1988**, *110*, 7737.
(18) Harp, D. N.; Aida, T.; Chan, T. H. *Tetrahedron Lett.* **1979**, 2853.
(19) (a) Herzig, J.; Nudelman, A.; Gottlieb, H. E. *Carbohyd. Res.* **1988**, *177*, 21. (b) Nudelman, A.; Herzig, J.; Gottlieb, H. E. *Carbohyd. Res.* **1987**, *162*, 145.
(20) Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.
(21) Farina, V. *J. Org. Chem.* **1991**, *56*, 4985.

Table 5. Cleavage of Benzyl, Benzhydryl, (Pivaloyloxy)methyl, and Thiol Esters

entry	starting ester	product	condns	yield[a] (%)
24	**46**	**20**	toluene, 80 °C, 48 h	70
25	**47**	**20**	toluene, 90 °C, 120 h	48
26	**48a** X = Br, Y = Br, n = 0	**49a**	ether, 25 °C, 5.5 h	47
27	**48b** X = H, Y = Cl, n = 0	**49b**	ether, 25 °C, 6 h	50
28	**48c** X = H, Y = OEt, n = 0	**49c**	ether, 25 °C, 3 h	56
29	**48d** X = H, Y = Cl, n = 2	**49d**	ether, 25 °C, 1 h	43
30	**48e** X = Br, Y = F, n = 0			*b*
31	**50**	**51** + **52**	acetonitrile, 80 °C, 2 h	57

[a] Isolated yields. [b] Decomposition of penam nucleus.

Table 6. Cleavage of Esters with Recovery of the Alcohols

entry	starting ester	product	condns	yield[a] (%)
32	**53**	**54**	benzene, 25 °C, 1.5 h	96
33	**55**	**56**	benzene, 80 °C, 8 h	92

[a] Isolated yields.

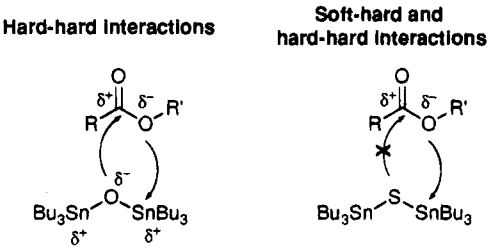
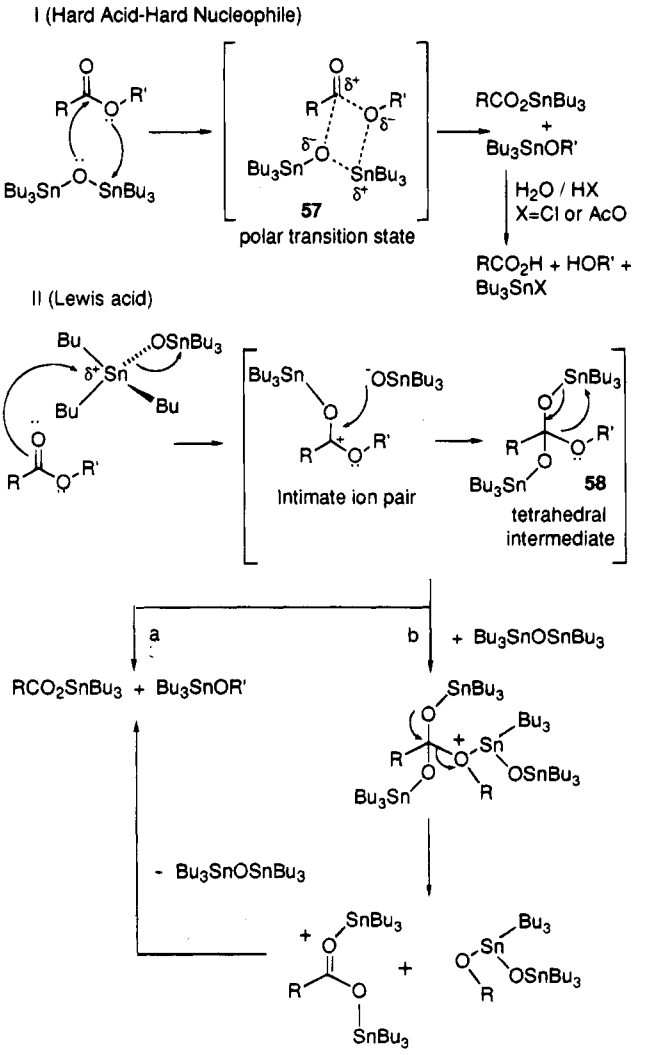


Figure 2.

exclusively (1*R*,2*S*,5*R*)-(−)-menthol (**39**) (see Table 3 and Experimental Section), we decided to test bis(tributyltin)-sulfide (BBTS), a softer analog of the BBTO reagent.[22] Thus, methyl benzoate (**19**) was not cleaved to benzoic acid (**20**) by BBTS, but was recovered quantitatively. As shown in Table 1, under identical experimental conditions using BBTO, benzoic acid was isolated in 80% yield. These results experimentally support the generality of our assumption by the necessity of a hard oxygen atom in BBTO for achieving the cleavage (Figure 2).

All the chemistry discussed above, including the effects of steric hindrance around carboxyl and carbinol centers and of steric congestion in BBTO reflected on the rate of cleavage, and the exclusive retention of configuration of **39** can be accommodated by two alternative mechanisms[23] (Scheme 1). Mechanism I involves the polar transition state (**57**), which implies that a nucleophilic hard oxygen coordinates on the hard electrophilic carbonyl carbon center, followed by or simultaneously with an attack of the hard nucleophilic oxygen of the carbinol moiety on the hard electrophilic tin atom. It is well known that tin attached to oxygen enhances the nucleophilicity of the latter without increasing its basicity.[24,25] The tri(butyltin) carboxylates[10] are readily hydrolyzed by aqueous acid or even during silica gel purification. The alcohols were liberated from the corresponding tri(butyltin) alkoxide[26] as indicated in the Experimental Section.

Scheme 1



Alternative mechanism II is based on Lewis acid complexation of BBTO[27] at the carboxyl oxygen atom. We propose that via ion-pair intermediate the tetrahedral intermediate **58** is generated and that it undergoes an elimination reaction (see path a), giving rise directly to tributyltin carboxylates and the corresponding tributyltin alkoxide. The fact that 2 equiv of BBTO are used in the reaction leads us to consider that the oxygen atom of carbinol center in intermediate **58** probably undergo coordination with a second molecule of BBTO (see path b) as shown in Scheme 1.[28]

(22) Formally, the hard oxygen atom is replaced by a soft sulfur atom. The hardness parameters (n) are 6.08 and 4.12, respectively. See ref 4f.

(23) While the mechanistic arguments presented here await further experimental verification, they do rationalize the discussed selective cleavage of carboxylic ester by BBTO.

(24) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643

(25) Reference 1, pp 269–277.

(26) For the preparation of tributyltin alkoxides by reacting BBTO with alcohols, see: Davies, A. G; Kleinschmidt, D.; Palan, P. R.; Vasishtha, S. C. *J. Chem. Soc.* **1971**, 3972.

(27) Qualitative estimation of the acidity of the BBTO was made by using the phosphine oxide IR frequency shift method, see: Vedejs, E.; Erdman, D. E.; Powell, D. R. *J. Org. Chem.* **1993**, *58*, 2840 and also see corrections in *J. Org. Chem.* **1993**, *58*, 6162.

(28) One of the reviewers commented on the mechanism II and suggested that path b should be considered.

Conclusion

The goals of the present investigation were to develop a method for the cleavage of methyl or ethyl aliphatic and aromatic carboxylic esters in aprotic solvents. This led to a mild and simple alternative to the hydrolysis by acidic or basic aqueous solutions, allowing now an even more frequent use of these simple esters as protecting groups in organic synthesis. Moreover, the near neutral pH insures the survival of common acid or alkali sensitive protecting groups as well as a variety of unprotected functional groups. The high degree of chemoselectivity of BBTO is evident from the selective deprotection of methyl and ethyl esters in the presence of a γ-lactone and *tert*-butyl esters. This procedure may be of more general utility for differential deprotection in molecules bearing multiple carboxylic esters.

Furthermore, (pivaloyloxy)methylcarboxylates, thiol esters, alcohols and phenolic hydroxyl groups protected as esters, are likewise cleaved with BBTO under mild conditions and the process is fast. It is also noteworthy from the cleavage of an ester of a chiral alcohol that this procedure is useful for the recovery of chiral alcohols with complete retention of configuration.

BBTO is commercially available and inexpensive.

We have found that this method has two limitations. One is that as the steric hindrance around the carboxyl and carbinol carbon increases, products are obtained in low yield, and the other is that BBTO is not suitable for cleaving esters in the presence of a fluoroalkyl group.

Experimental Section

All NMR spectra were measured in $CDCl_3$ at 80.13 and 200 MHz for protons and 20.15 or 50.3 MHz for ^{13}C. Optical rotations were measured on a polarimeter at ambient temperature using a 1-mL capacity cell. Column chromatography was performed on silica gel 60 A (100–200 mesh). Thin-layer chromatography (TLC) was done on silica gel GF_{254} (type 60, Merck). Compounds were visualized by UV light (254 nm), iodine, or by spraying with 5% ethanolic phosphomolybdic acid and then heating. Toluene was dried with $CaSO_4$, filtered, and distilled. Unless otherwise noted, other solvents were reagent-grade commercial materials and were freshly distilled.

Materials. Starting esters **1**, **3**, **7**, **9**, **11**, **13**, **15**, **17**, **19**, **21**, **25**, **27**, **38**, **40**, **44**, **46**, **50**, **53**, and **55** were obtained commercially and used without purification. Esters **5**,[29] **42**,[30] **47**,[31] **48a**,[32] **48b**,[32] **48c**,[33] **48d**,[32] and **48e**[34] are known. Esters **23**,[35] **28**,[36] **30**,[37] **32**,[38] **34**,[39] and **36**[40] were prepared from the commercially available parents acids **24**, **29**, and **31** or alcohols **33**, **35**, and **37** by standard procedures[41] and assayed by TLC and ^1H NMR analyses showed >98% purity. TLC and spectral analyses (IR, ^1H and ^{13}C NMR) indicated that all acids product were identical with authentic material or in agreement with those previously reported. Acids **4**, **6**, **10**, **20**, **22**, **24**, **26**, **29**, **31**, **51**, thiol **52**, phenol **54** and alcohols **39**, **56**, **33**, **35**, and **37** were obtained commercially. Acids **2**,[42] **8**,[43] **12**,[44] **14**,[45] **16**,[46] **18**,[46] **43**,[47] **45**,[48] **49a**,[49] **49b**,[50] **49c**,[51] and **49d**[52] are known.

General Procedure A. Cleavage of Methyl and Ethyl Esters (Table 1). (*R*)-3-Bromo-2-methylpropionic Acid (2). To a stirred solution of BBTO (0.72 mL, 1.4 mmol) in toluene (10 mL) was added methyl 3-bromo-2-methylpropionate (**1**) (130 mg, 0.72 mmol). The mixture was refluxed for 48 h and the solvent evaporated *in vacuo*. The resulting oil was dissolved in EtOAc (10 mL) and extracted with 5% aqueous $NaHCO_3$ (3 × 5 mL). The aqueous phase was acidified to pH 4–5 with dilute HCl and extracted with EtOAc (3 × 5 mL). The organic phase was washed with brine (2 × 5 mL), dried (Na_2SO_4), and evaporated *in vacuo* to afford **2** (69 mg, 60%), as an oil: $[\alpha]_D$ +9.5° (*c* 3.07 EtOH) (lit.[53] $[\alpha]_D$ +10° neat); IR (film) 3290, 2970, 1730, and 1390 cm^{-1}; ^1H NMR 1.34 (d, J = 7.2 Hz, 3H), 2.94 (m, 1H), 3.50 (dd, J = 6.4 and 10 Hz, 1H), 3.58 (dd, J = 12 and 10 Hz, 1H).

(*E*)-Cinnamic Acid (4). Acid **4** was obtained in 90% yield: mp 132–133 °C (lit.[54] mp 133 °C); ^1H NMR 6.45 (d, J = 16 Hz, 1H), 7.39–7.59 (m, 5H), 7.80 (d, J = 16 Hz, 1H).

4-Pentenoic Acid (6). Compound **6** was obtained in 42% yield: IR (film) 3290, 1750, and 1400 cm^{-1}; ^1H NMR 2.23–2.52 (m, 4H), 4.95–5.17 (m, 2H), 5.69–6.05 (m, 1H).

4-Bromo-2-butenoic Acid (8). Acid **8** was prepared in 70% yield: mp 72–73 °C (lit.[44] mp 74 °C); IR (KBr) 3100, 1690, 1420, and 1320 cm^{-1}; ^1H NMR 4.02 (dd, J = 8 and 1 Hz, 2H), 6.04 (dt, J = 15 and 1 Hz, 1H), 7.12 (dt, J = 15 and 8 Hz, 1H).

Phenylacetic Acid (10). Obtained in 95% yield: mp 76 °C (lit.[55] mp 76 °C); ^1H NMR 3.63 (s, 2H), 7.29 (br s, 5H).

(*R*)-(+)-2,2-Dimethyl-1,3-dioxolane-4-carboxylic Acid (12). Acid **12** was obtained in 48% yield: $[\alpha]_D$ +23° (*c* 2, H_2O) (lit.[56] $[\alpha]_D$ +23° (*c* 2, H_2O)); IR (film) 3345, 1730, and 1100 cm^{-1}; ^1H NMR 1.41 (s, 3H), 1.49 (s, 3H), 4.10 (dd, J = 4 and 7 Hz, 1H), 4.24 (dd, J = 7 and 8 Hz, 1H), 4.6 (dd, J = 4 and 8 Hz, 1H).

(4*S*)-(*Z*)-3-(Dimethyl-1,3-dioxolan-4-yl)-2-propenoic Acid (14). Compound **14** was obtained in 70% yield: IR (film) 3290, 1720, and 1170 cm^{-1}; ^1H NMR 1.40 (s, 3H), 1.45 (s, 3H), 3.61 (dd, J = 6.4 and 8 Hz, 1H), 4.37 (dd, J = 7.2 and 8 Hz, 1H), 5.35–5.61 (m, 1H), 5.87 (dd, J = 1.6 and 11.2 Hz, 1H), 6.51 (dd, J = 7.2 and 11.2 Hz, 1H).

Diethylmercaptoglyoxylic Acid (16). Compound **16** was obtained in 52% yield: IR (film) 3320, 1720, and 1430 cm^{-1};

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^{1}H NMR 1.29 (t, J = 7 Hz, 6H), 2.75 (q, J = 7 Hz, 4H), 4.37 (s, 1H).

1,3-Dithiolane-2-carboxylic Acid (18). Compound **18** was prepared in 52% yield: mp 86–88 °C (lit.[46] mp 91–92 °C); IR (film) 3220, 1690, 1320, and 930 cm^{-1}; ^{1}H NMR 3.4 (d, J = 2.4 Hz, 4H), 4.87 (s, 1H).

Benzoic Acid (20). Starting from methyl benzoate (**19**), acid **20** was obtained in 80% yield: mp 121–122 °C (lit.[57] mp 122–123 °C); ^{1}H NMR 7.45–7.55 (m, 3H), 8.06 (d, J = 1.6 Hz, 1H), 8.16 (s, J = 1.6 Hz, 1H).

Salicylic Acid (22). Acid **22** was obtained in 85% yield. Characterization gave data which agreed with those reported in the literature.[58]

(*S*)-5-Oxo-2-tetrahydrofurancarboxylic Acid (24). Prepared as described in the general procedure A with the following modifications. Acetonitrile was used as solvent and the reaction mixture was stirred at 60 °C for 24 h. After that, the solvent was evaporated *in vacuo* and the product **24** was isolated by C-18 reversed-phase silica gel column chromatography (eluent: acetonitrile–water): yield 55%; $[\alpha]_D$ +15° (*c* 4.5, MeOH) (lit.[59] $[\alpha]_D$ +16° (*c* 4.6; MeOH)); IR (film) 3350, and 1770 cm^{-1}; ^{1}H NMR 2.33–2.60 (m, 1H), 4.90–5.06 (m, 1H); ^{13}C NMR 25.69, 26.55, 75.05, 174.19, 175.88.

General Procedure B. Reaction of Methyl Carboxylic Esters Sterically Hindered Around the Carboxyl Carbon with BBTO (Table 2). Reaction of Methyl Pivalate (25) with BBTO. Methyl pivalate (**25**) (150 mg, 1.33 mmol) was added to a solution of BBTO (1.33 mL, 2.6 mmol) in toluene (10 mL). The mixture was refluxed for 72 h and the solvent evaporated *in vacuo*. TLC and ^{1}H NMR of the crude mixture showed the presence of starting material. This crude mixture was dissolved in EtOAc (10 mL) and extracted with 5% aqueous $NaHCO_3$ (3 × 5 mL). The aqueous layer was acidified to pH 4 with diluted HCl and extracted with EtOAc (3 × 5 mL). The organic layer was washed with brine (2 × 5 mL), dried (Na_2SO_4), and evaporated *in vacuo* to obtain **26** (7 mg, 5% yield) as a yellow oil. From the first organic phase after $NaHCO_3$ extraction, the starting ester **25** was recovered. Data for **26**: IR (film) 3320, 2980, and 1720 cm^{-1}; ^{1}H NMR 1.20 (s, 9H), 7.37 (br s, 1H).

Reaction of Methyl 1-Adamantanecarboxylate (28) with BBTO. 1-Adamantanecarboxylic acid (**29**) was obtained with 10% and the starting material recovered. Data for **29**: ^{1}H NMR 1.70 (br s, 5H), 1.90–2.0 (m, 10H); ^{13}C NMR 27.82, 36.37, 38.72, 178.06.

Reaction of Methyl 1-Adamantaneacetate (30). 1-Adamantaneacetic acid (**31**) was obtained in 25% yield and the starting material recovered. Data for **31**: ^{1}H NMR 1.66 (br s, 12H), 1.98 (br s, 3H), 2.1 (s, 2H); ^{13}C NMR 28.51, 32.57, 36.59, 42.18, 48.61, 178.11.

General Procedure C. Cleavage of Methyl and Ethyl Esters of Mixed Diesters in the Presence of *tert*-Butyl Esters (Table 4). Synthesis of *tert*-Butyl Succinate Monoacid (43). *tert*-Butyl methyl succinate (**42**) (187 mg, 1 mmol) was added to a solution of BBTO (1 mL, 1.95 mmol) in toluene (10 mL). This mixture was stirred at 80 °C for 14 h and then the solvent was evaporated *in vacuo*. Workup already described for compound **2** was followed, obtaining **43** (121 mg, 70%) as an oil: IR (film) 3380, 1770, 1420, and 1200 cm^{-1}; ^{1}H NMR 1.45 (s, 9H), 2.56–2.62 (m, 4H).

***tert*-Butyl Malonate Monoacid (45).** Starting from *tert*-butyl ethyl malonate (**44**), compound **45** was obtained in 47% yield: IR (film) 3320, 1720, 1365, and 1150 cm^{-1}, ^{1}H NMR 1.49 (s, 9H), 3.34 (s, 2H).

Cleavage of Benzyl Esters. Preparation of Benzoic Acid (20) (Table 5). Benzyl benzoate (**46**) (100 mg, 0.47 mmol) was added to a solution of BBTO (0.47 mL, 0.92 mmol) in toluene (10 mL). The mixture was heated at 80 °C for 48 h and then the solvent was evaporated *in vacuo*. Workup already described for compound **2** was followed. Benzoic acid (**20**) was obtained in 70% yield as white crystals. For data, *vide supra*.

Cleavage of Benzhydryl Esters. Preparation of Benzoic Acid (20) (Table 5). Benzhydryl benzoate (**47**) (150 mg, 0.519 mmol) was added to a solution of BBTO (0.52 mL, 1.01 mmol) in toluene (10 mL). The mixture was heated at 90 °C for 120 h and the solvent evaporated *in vacuo*. The same workup described for compound **2** was followed, yielding 48% (64.0 mg) of **20** and recovering 40% of starting material. Data for **20**, *vide supra*.

General Procedure D. Cleavage of Pom Penicillanate Esters (Table 5). Preparation of 6,6-Dibromopenicillanic Acid (49a). A mixture of Pom 6,6-dibromopenicillanate (**48a**) (47.3 mg, 0.1 mmol) and BBTO (0.1 mL, 0.2 mmol) in ether (2.5 mL) was stirred at 25 °C. The progress of the reaction was monitored by TLC to check for the disappearance of the starting material. At the end of the reaction (5.5 h), the solvent was evaporated *in vacuo*, and the crude material was prepurified by preparative TLC (eluent: ether–hexane–formic acid, 50:50:0.1) to remove pivalic acid and most of the organotin compounds. Then, hexane (2 mL) was added to the impure product and extracted with 5% aqueous $NaHCO_3$ (3 × 1.5 mL). The combined aqueous layers were acidified, extracted with EtOAc (3 × 2 mL), and dried (Na_2SO_4). Removal of the solvent afforded pure acid (**49a**) (17mg, 47%), as a crystalline solid: mp 144–146 °C (lit.[60] mp 144–146 °C); IR (KBr) 3240, 1790, and 1770 cm^{-1}; ^{1}H NMR 1.56 (s, 3H), 1.65 (s, 3H), 4.57 (s, 1H), 5.78 (s, 1H).

6α-Chloropenicillanic Acid (49b). Using similar conditions, but without prepurification, acid **49b** was obtained in 50% yield (measured by ^{1}H NMR from the mixture with pivalic acid): ^{1}H NMR 1.57 (s, 3H); 1.63 (s, 3H), 4.56 (s, 1H), 4.77 (d, J = 1.6 Hz, 1H), 5.33 (d, J = 1.6 Hz, 1H).

6α-Ethoxypenicillanic Acid (49c). Following the general procedure D, excluding prepurification, compound **49c** was prepared in 56% yield (measured by ^{1}H NMR from the mixture with pivalic acid): ^{1}H NMR 1.24 (t, J =7.2 Hz, 3H), 1.55 (s, 3H), 1.6 (s, 3H), 3.59–3.87 (m, 2H), 4.5 (s, 1H), 4.62 (d, J = 1.6 Hz, 1H), 5.28 (d, J = 1.6 Hz, 1H).

6α-Chloropenicillanic Acid 1,1-Dioxide (49d). Following the general procedure D, excluding prepurification, compound **49d** was obtained in 43% yield (measured by ^{1}H NMR from the mixture with pivalic acid): ^{1}H NMR 1.51 (s, 3H), 1.64 (s, 3H), 4.46 (s, 1H), 4.67 (d, J = 1.6 Hz, 1H), 5.17 (d, J = 1.6 Hz, 1H).

Cleavage of 2-Mercaptobenzothiazolyl (2-Aminothiazol-4-yl)-2-(methoxyimino)thioacetate (50) (Table 5). Synthesis of (2-Aminothiazol-4-yl)-2-(methoxyimino)acetic Acid (51) and 2-Mercaptobenzothiazole (52). Thiol ester **50** (500 mg, 1.43 mmol) was added to a solution of BBTO (1.48 mL, 2.87 mmol) in acetonitrile (10 mL). The reaction mixture was heated at 80 °C for 2 h and then the solvent was evaporated *in vacuo*. The crude mixture was extracted with 5% aqueous $NaHCO_3$ (3 × 10 mL). The aqueous phases were acidified to pH 4–5 with diluted HCl and then extracted with EtOAc (3 × 10 mL). Purification by column chromatography (eluent: $CHCl_3$/MeOH, 65:35; then MeOH) afforded compounds **51** (163 mg) and **52** (80 mg) as oils, yield 57%. Data for **51**: IR (film) 3470, 3100, 1760, and 1630 cm^{-1}; ^{1}H NMR 3.74 (s, 3H), 5.38 (br s, 2H), 6.27 (s, 1H). Data for **52**: IR (film) 2980, 1590, and 940 cm^{-1}; ^{1}H NMR 7.32–7.98 (m, 4H).

General Procedure E. Cleavage of Esters with Recovery of the Alcohols (Tables 3 and 6). 5-(Hydroxymethyl)furaldehyde (56). To a solution of 5-(acetoxymethyl)-2-furaldehyde (**55**) (150 mg, 0.88 mmol) in benzene (10 mL) was added BBTO (0.9 mL, 0.775 mmol). The mixture was stirred at 80 °C for 8 h and concentrated *in vacuo*. The residue was purified by preparative TLC yielding **56** (103 mg, 92%) as a crystalline solid: mp 30 °C (lit.[61] mp 32–35 °C); IR (film)

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3320, 2980, and 1740 cm^{-1}; ^1H NMR 4.71 (s, 2H), 6.49–6.54 (d, J = 4.0 Hz, 1H), 7.20–7.24 (d, J = 4.0 Hz, 1H), 9.57 (s, 1H).

1-Adamantaneethanol (33). Compound **33** was obtained in 97% yield: mp 67–69 °C (lit.[62] mp 66–69 °C); ^1H NMR 1.41 (t, J = 7 Hz, 2H), 1.52–1.67 (m, 13H), 1.93 (br s, 3H), 3.71 (t, J = 7 Hz, 2H); ^{13}C NMR 27.9, 37.16, 37.5, 47.81, 74.9.

1-Adamantanemethanol (35). Compound **35** was obtained in 97% yield: mp 109–111 °C (lit.[62] mp 115–118 °C); ^1H NMR 1.50–1.77 (m, 13H), 1.99 (br s, 3H), 3.20 (s, 2H); ^{13}C NMR 28.03, 37.02, 38.88, 73.58.

1-Adamantanol (37). Compound **37** was obtained in 15% yield as an oil, and starting material **36** was recovered in 70%: ^1H NMR 1.62–1.73 (m, 12H); 2.13 (br s, 3H); ^{13}C NMR 28.03, 37.01, 38.88, 73.58.

(−)-(1*R*) Menthol (39). Menthyl acetate (**38**), $[\alpha]_D$ −80° (*c* 8, benzene) (643 mg, 3.25 mmol), was heated under reflux in toluene containing BBTO (3.2 mL, 6.50 mmol) for 24 h. Column chromatography (silica gel, eluent: hexane/EtOAc, 70:30) afforded the impure product. Quantitative removal of the organotin residues was achieved by stirring a dichloromethane solution (10 mL) with 40% HF (10 mL) for 2 h at room temperature. The organic layer was extracted with brine (3 × 10 mL) and dried with Na_2SO_4. Removal of the solvent yielded pure (−)-(1*R*)-menthol (**39**), (319.2 mg, 63%): $[\alpha]_D$ −49° (*c* 1, EtOH) (lit.[58] $[\alpha]_D$ −50° (*c* 10, EtOH)); mp 40–42 °C (lit.[31] mp 41–43 °C); IR (KBr) 3480, 2980, and 1230 cm^{-1}, ^1H NMR 0.77–0.97 (m 18H), 3.26–3.61 (m, 1H); ^{13}C NMR 15.9, 20.78, 21.96, 23.02, 25.61, 31.49, 34.37, 44.90, 49.96, 71.25.

Endo-(1*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol (41). (−)-Bornyl acetate (**40**) (100 mg; 0.51 mmol) was heated under reflux in acetonitrile containing BBTO (0.51 mL, 0,99 mmol) for 96 h. Workup already described for alcohol **39** was followed, obtaining **41** (10 mg, 12.7%) as a crystalline solid: mp 202–204 °C (lit.[62] mp 206–208 °C), and starting material was recovered in 81%.

4-Nitrophenol (54). To a solution of BBTO (0.55 mL, 0.474 mmol) in benzene (10 mL) was added 4-nitrophenyl acetate (**53**) (100 mg, 0.55 mmol). The mixture was stirred for 1.5 h at room temperature and the solvent evaporated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and extracted with 5% aqueous $NaHCO_3$ (2 × 5mL) and then with 10% aqueous NaOH (3 × 5 mL). The NaOH extract was acidified to pH 4–5 with diluted HCl and then extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. Compound **54** was obtained in 96% yield (73.7 mg) as white crystals: mp 111–113 °C (lit.[58] mp 113–114 °C); IR (KBr) 3270, 1590, 1330, and 730 cm^{-1}; ^1H NMR 6.91 (d, J = 9.61 Hz, 2H), 8.17 (d, J = 9.61 Hz, 2H).

Acknowledgment. We thank CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) for financial support. C.J.S. thanks CIUNR (Consejo de Investigaciones Universidad Nacional de Rosario) for a fellowship. We also thank to Professor Heinz G. Floss for helpful comments on the manuscript.

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