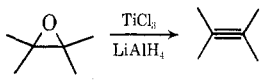
Table I
Reduction of Epoxides to Olefins with $TiCl_3$–$LiAlH_4$

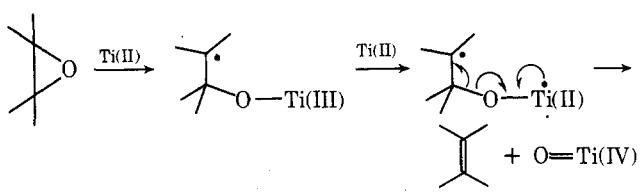


Substrate	Registry no.	Yield, %	Registry no.
α-Methylstyrene oxide	2085-88-3	36	98-83-9
Cyclooctene oxide	286-62-4	53	931-88-4
1-Dodecene oxide	2855-19-8	69	112-41-4
1-Decene oxide	2404-44-6	65	872-05-9
Cholesterol oxide	55700-78-2	75	57-88-5
cis-5-Decene oxide	36229-64-8	70 (4:1 trans/cis)	7433-78-5 (cis)
trans-5-Decene oxide	2165-61-9	70 (4:1 trans/cis)	7433-56-9 (trans)

metal salts including chromous ion,[2] zinc–copper couple,[3] magnesium amalgam,[4] zinc,[5] low valent tungsten complexes,[6] and $FeCl_3$–BuLi.[7] We have recently been studying the use of low valent titanium species as reducing agents for organic systems[8] and therefore examined the possible reduction of some epoxides.

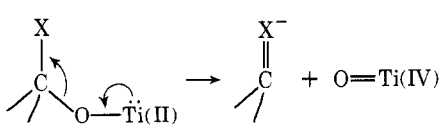
We have found that Ti(II), prepared by reaction of dry $TiCl_3$ with 0.25 molar equiv of $LiAlH_4$ in tetrahydrofuran, is a convenient and efficient reagent for converting epoxides to olefins. Some of our results are given in Table I.

The mechanism of epoxide reduction with Ti(II) is probably similar to that proposed by Kochi[2] for the chromous ion reduction. Central to this postulate is the implication



that the reaction must proceed with loss of olefin stereochemistry, as observed for reductions with chromous ion[2] and ion,[7] but not with low-valent tungsten.[6] This is in fact observed as shown in Table I. Both *cis*- and *trans*-5-decene oxide give the identical 81:19 mixture of *trans*- and *cis*-5-decene on treatment with $TiCl_3$–$LiAlH_4$. A control experiment established the stability of *cis*-5-decene under the reaction conditions.

Yet a further implication of this mechanistic postulate is the expectation that whenever a Ti(II)–oxygen bond is formed next to a group, X, which can stabilize free radicals, then deoxygenation should occur. We have confirmed this expectation in reactions with halohydrins (X = CBr) and cyanohydrins (X = CN), and we are currently studying these and other cases in detail.[9]



From a synthetic point of view, use of $TiCl_3$–$LiAlH_4$ for epoxide reduction appears competitive with use of other reagents. A major advantage of the present procedure, however, is the ease with which the reagent may be prepared. A 4:1 ball-milled mixture of $TiCl_3$ and $LiAlH_4$ prepared for our evaluation by Alfa Inorganics has proven to be indefinitely stable in the absence of solvent and extremely convenient to use as a one-bottle source of reagent.[10]

Experimental Section

General Reaction Procedure. The titanium reagent was prepared in either of two ways.

Method A. Lithium aluminum hydride (0.20 g, 5.0 mmol) was added in small portions to a stirred slurry of $TiCl_3$ (3.08 g, 20.0 mmol) in 60 ml of dry tetrahydrofuran under an inert atmosphere (argon or nitrogen) at room temperature. Hydrogen evolution was immediate, and the resulting fine black suspension was stirred for 15 min before use.

Method B. Alternatively, a 4:1 premix of $TiCl_3$ and $LiAlH_4$[10] (effective mol wt 164, 3.28 g, 20.0 mmol) was added with stirring and in small portions to 60 ml of dry THF at room temperature under an inert atmosphere. Hydrogen evolution occurred immediately and the fine black suspension was stirred 15 min before use.

A solution of epoxide (10 mmol) in 10 ml of dry THF was added to the Ti(II) reagent, and the reaction mixture was refluxed for 3 hr. The reaction mixture was then cooled to room temperature and quenched by addition of 60 ml of water. The organic layer was diluted with ether, then drawn off, washed with water and with brine, dried ($MgSO_4$), and concentrated to yield the product. With the exception of cholesterol, yields were determined by GLC with appropriate internal standards added. Products were identified by comparison with authentic samples. The results are presented in Table I.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this work.

References and Notes

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(10) We thank Mr. Robert Wade, Alfa Inorganics, Beverly, Mass., for preparing this premix, which is commercially available as "Mc Murry's Reagent".

A Simple One-Step Alternative to the Malonic Ester Synthesis

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The classical malonic ester synthesis involving discrete alkylation and decarbalkoxylation steps remains, in spite of attempts at replacement, the standard method for effecting two-carbon homologation of alkyl halides. Although nor-

Table I
Reaction of Alkyl Halides with the Dilithium Salt of Monoethyl Malonate
$RX + LiCH(COOLi)COOEt \rightarrow RCH_2COOEt$

RX		RCH_2COOEt		Yield, %[a]
Methallyl chloride	563-47-3	$CH_2{=}C(CH_3)CH_2CH_2COOEt$	4911-54-0	71
Allyl bromide	106-95-6	$CH_2{=}CHCH_2CH_2COOEt$	1968-40-7	80
Benzyl chloride	100-44-7	$PhCH_2CH_2COOEt$	2021-28-5	75
Ethyl chloroacetate	105-39-5	Diethyl succinate	123-25-1	98
Chloroacetone	78-95-5	$CH_3COCH_2CH_2COOEt$	539-88-8	25
Ethyl iodide	75-03-6	$CH_3CH_2CH_2COOEt$	105-54-4	60
n-Butyl bromide	109-65-9	$CH_3(CH_2)_4COOEt$	123-66-0	80
n-Decyl bromide	112-29-8	$CH_3(CH_2)_{10}COOEt$	106-33-2	60
2-Bromopropane	79-26-3	$(CH_3)_2CHCH_2COOEt$	108-64-5	50
2-Bromobutane	78-76-2	$CH_3CH_2CH(CH_3)CH_2COOEt$	5870-68-8	22

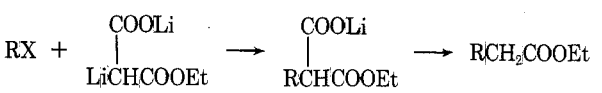
[a] Yields given represent distilled product.

mally a three-step alkylation, saponification, decarboxylation sequence is used,[1] a recently introduced variation, in which decarbalkoxylation can be effected in a single step, seems to give better overall yields.[2]

Ideally, one could simplify the procedure still further by alkylating directly with lithio ethyl acetate, but this does not seem to be feasible. Lithio ethyl acetate can be readily prepared at −78° and caused to undergo aldol addition to simple carbonyl compounds.[3] In reaction with alkyl halides, however, it reacts poorly, giving the product in 20–30% yields.[4] Lithio *tert*-butyl acetate seems to alkylate well,[4] but the use of *tert*-butyl esters can introduce unwanted complications in synthesis.

A further possibility is the alkylation of an acid dianion according to Creger's method,[5,6] but again this does not seem to be feasible. Although the dianions of substituted acetic acids alkylate well, especially when the solvent modification of Pfeffer and Silbert is used,[7,8] the parent dilithioacetate reacts poorly. Even were this reaction to go well, a separate esterification step would be required.

We reasoned that these difficulties could be resolved, and the malonic ester synthesis simplified considerably, if one were to alkylate with the dianion of monoethyl malonate. On simple warming of the reaction, the intermediate alkylated monoethyl malonate should decarboxylate, giving the desired product directly. The starting material is readily available by partial saponification of diethyl malonate.[9]



The expected reaction does in fact proceed as planned, giving the ester products in fair to excellent yields. Some of our results are given in Table I.

As can be seen from Table I activated halides (R = allylic, benzylic) alkylate in excellent yields. Primary halides also give good results, but, as expected, secondary halides react less well.

In summary, we feel that this new method is clearly superior to the classical malonic ester synthesis both in yield and in ease of operation, and we expect that it will find use in synthesis.

Experimental Section

General Reaction Procedure. Isopropylcyclohexylamine (4.15 g, 29.4 mmol) was dissolved in 10 ml of dry tetrahydrofuran (THF) under a nitrogen atmosphere, and the temperature of the solution was lowered to −78° by means of a Dry Ice bath. *n*-Butyllithium (14.3 ml of 2.06 *M* solution in hexane, 29.4 mmol) was then added via syringe. Monoethyl malonate (1.94 g, 14.7 mmol) in 10 ml of THF was added, and the reaction was allowed to warm to ice temperature to form the dianion. After 15 min of stirring, 4.0 ml of dry hexamethylphosphoramide was added, followed by addition of the alkyl halide (14.7 mmol) in 5 ml of dry THF. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hr to effect alkylation. After this time the reaction mixture was refluxed (68°) overnight to effect decarboxylation.

After cooling, the reaction mixture was poured into water and extracted with ether. The ether extracts were washed with dilute hydrochloric acid, with saturated sodium bicarbonate, and with brine, then dried ($MgSO_4$), filtered, and concentrated at the rotary evaporator. The residue was distilled to yield the product.

Product identification was made through a combination of spectroscopic methods (ir, NMR, mass spectra) and through comparison of the product boiling points with literature values.

Acknowledgment. We thank the National Institutes of Health for their support of this work through Grant CA11277.

Registry No.—Monoethyl malonate, 1071-46-1.

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Complete Stereochemistry of Tenulin. Carbon-13 Nuclear Magnetic Resonance Spectra of Tenulin Derivatives

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Determination of the gross structure of the sesquiterpene lactone tenulin (1)[1] was an early example of the successful use of ^1H NMR spectrometry in natural products chemistry. Subsequently, the relative and absolute configuration of tenulin at C-1, C-5, C-7, and C-10 was deduced by