Pergamon

Tetrahedron Letters 41 (2000) 6399–6402

TETRAHEDRON LETTERS

A convenient approach to substituted 1-(1-alkenyl)cyclopropanols: a new preparation of 2,3-methanoamino acids

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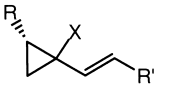
Received 24 May 2000; accepted 27 June 2000

Abstract

The diastereoselective titanium(IV)-mediated cyclopropanation of ethyl 3,3-diethoxypropionate by Grignard reagents, followed by modified Knoevenagel condensation with malonic acid under microwave irradiation, allow the preparation of (*E*)-1-(1-alkenyl)cyclopropanol derivatives, suitable precursors of π-1,1-dimethyleneallylmetal species. The azidation of such complexes, followed by a reduction–oxidation sequence led to pure (*E*)-2,3-methanoamino acids.

Keywords: titanacyclopropanes; π-1,1-dimethyleneallylpalladium complexes; azidation; microwave irradiation.

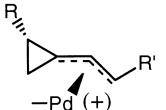
Cyclopropane derivatives provide building blocks of unprecedented synthetic potential;[1] moreover, natural and synthetic cyclopropanes bearing simple functionalities (hydroxy, amino, carboxylic acid groups, nucleic bases, etc.) are endowed with a large spectrum of biological properties.[2] Therefore new methods for the construction of functionally substituted cyclopropane derivatives are of significant interest and are under current investigations.



R, R'= H, alkyl, SiR''_3

1a X=OH

b OTs, OMs



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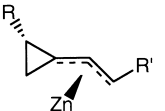

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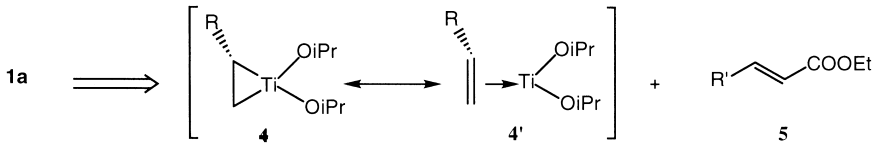
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01089-3

One of the flexible ways to such compounds is based on the reactions of organometallic species generated from 1-(1-alkenyl)cyclopropanols **1a** and their corresponding sulfonic esters **1b** (X = OTs, OMs), which revealed unexpected synthetic usefulness. Thus, upon treatment with a catalytic amount of palladium(0), esters **1b** form π-1,1-dimethyleneallylpalladium complexes **2**, which then react either with soft nucleophiles (e.g. enolates, hydroxides, amines and Schiff bases, etc.) to provide alkylidenecyclopropanes, or with hard nucleophiles (hydrides, azides, organometallic reagents, etc.) to lead to (1-alkenyl)cyclopropanes regio- and diastereoselectivity.[3] Furthermore, treatment of **2** with 2 equiv. of diethylzinc produces 1,1-dimethyleneallylzinc complexes **3**, which then undergo electrophilic substitutions by carbonyl compounds, regioselectively.[4] Highly useful synthetic applications of these metal complexes have recently been reported.[5a–g]

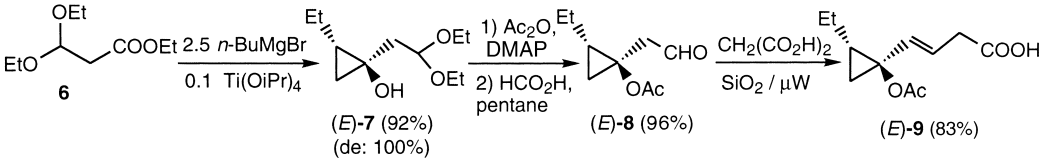
The required precursors **1a** were previously available either from cyclopropanone hemiacetals,[6] or from 1-hydroxycyclopropanecarboxylic acids.[7] As a possible alternative we have investigated the cyclopropanation of the α,β-unsaturated esters **5** by the methyltitanacyclopropanes **4**, also to be considered as the η^2-propylene Ti(O*i*Pr)$_2$ complexes **4′** (Scheme 1), arising from the reaction of titanium(IV)tetraisopropoxide with an excess of Grignard reagents. In fact, the titanium(IV) isopropoxide catalyzed reaction of organomagnesium compounds with alkanecarboxylates offers, without doubt, the most efficient procedure for the preparation of substituted cyclopropanols.[8,9] In addition, cyclopropylamines,[10,11] 1-(phosphorylalkyl)cyclopropanols and 1-acetonylaminocyclopropanes,[12] as well as other functionally substituted cyclopropanols and natural products have been obtained readily following this new strategy.[13] However, applying this method to α,β-unsaturated esters under various experimental conditions, the expected 1-ethenylcyclopropanols **1a** were obtained in low yields (10–25%).[14]



Scheme 1.

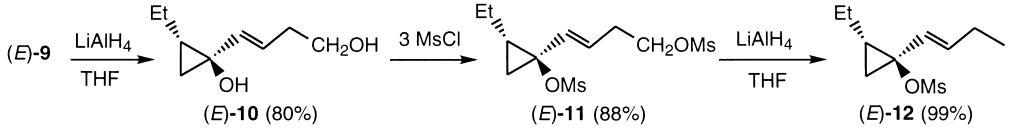
A possible reason for the low yields obtained for this cyclopropanation might originate from the further transformation of allylic alcohols such as **1a** by the titanacyclopropane reagent **4**, namely by the observed reductive elimination and alkyl substitution of the allylic hydroxy group.[15]

In order to overcome this problem we investigated the titanacyclopropane-mediated cyclopropanation of the commercially available ethyl 3,3-diethoxypropionate **6** (Scheme 2). Thus, upon simple reaction with 2.5 equiv. of *n*-BuMgBr in dimethoxymethane, in the presence of 0.1 equiv. of Ti(O*i*Pr)$_4$, the acetalester **6** led diastereoselectively to the (*E*)-1-(2,2-diethoxyethyl)-2-ethylcyclopropanol **7**, in 92% yield.[16] O-protection of (*E*)-**7** with acetic anhydride in diethyl ether containing 1.1 equiv. of DMAP, and deacetalization (HCOOH/pentane) provided the aldehyde (*E*)-**8** in 96% overall yield. Modified Knoevenagel condensation of (*E*)-**8** with a three molar excess of malonic acid in the presence of 0.001 M of piperidine,[17] in refluxing xylene for 2 h, led to the 4-(1-acetoxy-2-ethyl-cyclopropyl)but-3-enoic acid (*E*)-**9** in 40% yield. However, this β,γ-unsaturated acid was obtained more readily and in higher yield (83%) when equimolar quantities of aldehyde (*E*)-**8** and malonic acid adsorbed on silica gel were subjected to microwave irradiation (300 W) at 130°C for 15 min.[18]



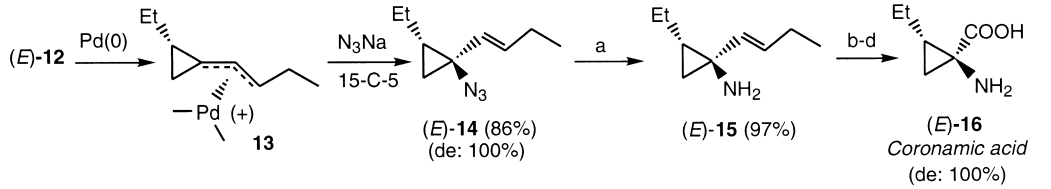
Scheme 2.

Lithium aluminum hydride reduction of (*E*)-**9** in THF, then provided the diol (*E*)-**10** (80% yield), which upon reaction with mesyl chloride (3 equiv.; NEt_3/Et_2O) gave the dimesylate (*E*)-**11** in 88% yield (Scheme 3). Partial reduction of (*E*)-**11** ($LiAlH_4$, THF), finally produced the expected 1-(1-butenyl)-2-ethylcyclopropyl mesylate (*E*)-**12** in 99% yield.



Scheme 3.

Palladium(0)-catalyzed [$Pd(dba)_2$, $2PPh_3$] azidation of (*E*)-**12** in the presence of 15-crown-5 ether (10%), which was proved to occur with complete retention of configuration via π-1,1-dimethyleneallyl-palladium complexes such as **13**,[5c] gave in 86% yield the single (*E*)-cyclopropylazide **14** (de: 100%; Scheme 4). Following a reported procedure,[5c] azide reduction [$HS(CH_2)_3SH$, $MeOH/NEt_3$] provided the amine (*E*)-**15**[19] and oxidative cleavage of the double bond ($RuCl_3/NaIO_4$) of (*E*)-**15** led to the racemic coronamic acid (*E*)-**16**.[20]



Scheme 4. (a) $HS(CH_2)_3SH$, MeOH, Et_3N; (b) BOC_2O, H_2O, *t*-BuOH, KOH; (c) $RuCl_3$, $NaIO_4$; (d) HCl, Dowex

In conclusion, the exclusive formation of the azide (*E*)-**14** and of the 2,3-methanoamino acid (*E*)-**16** proved the diastereoselectivity of the synthesis of the cyclopropanol (*E*)-**7** and therefore, of the substituted cyclopropanol derivatives **8**–**12**. The application of this new strategy to asymmetric substrates is under current investigation.

Acknowledgements

This work was financially supported by the CNRS and the Université de Paris-Sud (XI), by the INCO-COPERNICUS programme of cooperation of the European Community, for a project called 'A new protocol for sustainable environmental management (PROSEM)'.

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