Mild, Efficient Trimethylaluminum-Mediated Cyclopropanations. An Innovative Synthesis of the New Dehydrogenase Inhibitor Spiropentaneacetic Acid

Jennifer M. Russo† and William A. Price*

Department of Chemistry and Biochemistry, La Salle University, Philadelphia, Pennsylvania 19141

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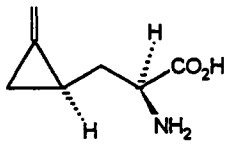
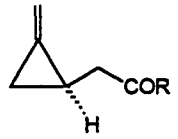
In recent years, in-depth studies have been carried out detailing the irreversible inactivation of general acyl-CoA dehydrogenase enzymes by (methylenecyclopropyl)acetyl CoA (MCPA-CoA, **1a**).[1-3] The free carboxylic acid, specifically (*R*)-(−)MCPA (**1b**)[3] is the toxic metabolite of hypoglycin-A, an amino acid found in the fruit of the Jamaican ackee tree. Ingestion of the unripe fruit is known to cause Jamaican vomiting sickness, a severe hypoglycemic response due to impaired fatty acid oxidation.[4]



Hypoglycin-A

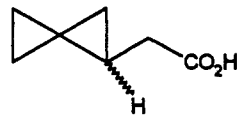


1a) R = SCoA, MCPA-CoA
1b) R = OH, MCPA

Over the past decade, several inherited defects of mitochondrial fatty acid oxidation have been identified that are biochemically comparable to induced Jamaican vomiting sickness.[5] Those patients affected may show episodes of acute life-threatening attacks that can resemble Reye's syndrome. The most common of these inborn errors of metabolism is known as medium chain acyl-CoA dehydrogenase (MCAD) deficiency.

In order to establish an effective animal model for these inherited abnormalities, we required an inhibitor similar to MCPA (**1b**), but specific for MCAD enzymes. Recently, such a compound was described;[6] spiropentaneacetic acid (SPA, **2**), a serendipitous byproduct in Hoppel's prepa-

2 (±) SPA



ration of racemic **1b**, appears to be a suicide substrate specifically for MCAD both *in vitro* and *in vivo*. The question of stereospecificity with regard to the inactivation by SPA has not yet been investigated.

Here we report the rapid, clean preparation of racemic SPA (**2**) from 3-butyn-1-ol (**3**). With a limited number of literature methods detailing the synthesis of spiropentyl systems,[7-9] we began by investigating the exhaustive cyclopropanation of an appropriately substituted allene. Our starting material, 3,4-pentadien-1-ol (**4**) was prepared using a modification of Crabbé's Cu(I)-catalyzed procedure.[10] The convenient one-pot homologation of alkyne **3** occurred smoothly in the presence of paraformaldehyde (2.5 equiv), diisopropyl amine (2.0 equiv) and CuI (0.5 equiv) in refluxing THF.[11] With ready access to significant quantities of **4**, we were able to explore a wide variety of cyclopropanation methods.

Carbenoid reactions with allenes (e.g. diazomethane or Simmons–Smith[12]) although chemically intriguing, have traditionally proven to be of little synthetic use due to the formation of mixtures of regioisomers, the need for a significant molar excess of carbene, and poor percent conversion of the starting allenes.[7-9] Attempts at utilizing diethylzinc/methylene iodide gave a number of the problems listed above as well as varying amounts of the corresponding methyl ether.

The use of trimethylaluminum/methylene iodide[13] seemed particularly well-suited to the dual methylenation of allene **4**. The apparent cyclopropanation species in this reaction, dimethyl(iodomethyl)aluminum, is stable in the presence of excess trimethylaluminum. In contrast, the corresponding species derived from triethyl- and triisobutylaluminum undergo decomposition under the same conditions. Thus, in the presence of trimethylaluminum (2 M in hexanes, 3.5 equiv, 1 equiv to complex with the alcohol) and methylene iodide (2.5 equiv) in methylene chloride, **4** was smoothly converted in 71% yield to (2-hydroxyethyl)spiropentane (**5**) in 16 h at room temperature (Scheme I). There were no monocyclopropanation products nor any starting allene detected in the crude product by gas chromatographic analysis.

Alternatively, alcohol **5** can be prepared from 2-(methylenecyclopropyl)ethanol (**6**) under similar reaction conditions (2.2 equiv of trimethylaluminum, 2 M in hexanes, 1.2 equiv methylene iodide, 72% yield). Alcohol **6** is most efficiently prepared by condensing (methylenecyclopropyl)lithium with ethylene oxide according to the procedure of Liu.[1] However, the volatility, expense, and lack of consistent commercial availability of methylenecyclopropane as well as the health hazard associated with ethylene oxide made this a less attractive approach.

Since alcohol **6** had been smoothly oxidized to MCPA (**1b**) using Jones reagent at low temperature,[1,2] we envisioned an analogous approach to SPA (**2**) from alcohol **5**. Unfortunately, use of this method resulted in extensive decomposition of the spiropentyl residue. Since the ring strain of alcohol **5** apparently requires the use of nonacidic

† Current address: Department of Biochemistry, University of North Carolina, Chapel Hill, NC 27516.

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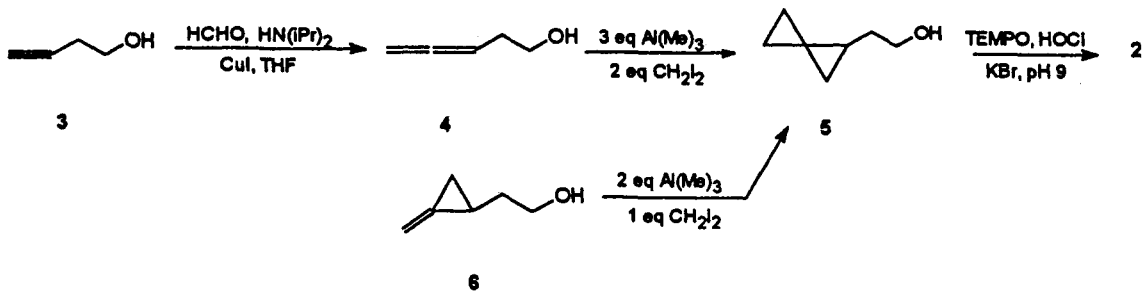
0022-3263/93/1958-3589$04.00/0

Scheme I



conditions, a buffered bleach-oxammonium salt combination[14] was employed to carry out the oxidation. In a biphasic bleach (0.40 M)/methylene chloride system, compound 5 was efficiently oxidized to SPA (2) using a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) as the source of the continually regenerated oxammonium salt (92%, 10 min).[15]

The preparation of SPA, while necessary from a medicinal standpoint, has in course unveiled a potentially valuable synthetic method. The efficient dual cyclopropanation of an allene and subsequent oxidation of a proximate hydroxyl group while maintaining the integrity of the highly strained ring system have been effectively demonstrated here.

Experimental Section

General. All materials were obtained from commercial sources and used without further purification. The bleaching power (molarity) of sodium hypochlorite (bleach) was determined by iodometry prior to use. Tetrahydrofuran (THF) was distilled from sodium–benzophenone, and dichloromethane was distilled from CaH_2 immediately prior to use. ^1H NMR and ^{13}C NMR spectra were obtained at 200.13 and 50.32 MHz, respectively, in $CDCl_3$ solutions. Infrared spectra were obtained as neat liquids.

3,4-Pentadien-1-ol (4). The procedure of Price[11] was used for the preparation of compound 4: ^1H NMR ($CDCl_3$, 200 MHz) δ 5.22 (tt, 1H, J = 6.8, 6.8), 4.81 (m, 2H), 3.79 (t, 2H, J = 6.6), 2.37 (9-line m, 2H), 1.80 (variable shift, br s, 1H, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 208.90, 86.34, 74.93, 61.69, 31.42.

Cyclopropanations: (2-Hydroxyethyl)spiropentane (5) from 3,4-Pentadien-1-ol (4). A solution of alcohol 4 (1.51 g, 17.9 mmol) and diiodomethane (12.00 g, 44.7 mmol) in 30 mL of CH_2Cl_2 was cooled to 0 °C under a nitrogen atmosphere. A 2.0 M hexane solution of trimethylaluminum (32.2 mL, 64.3 mmol) was added dropwise over 20 min; the first equivalent (approximately 10 mL) was added very slowly due to the exothermic formation of the aluminum alkoxide. The clear, colorless reaction mixture was stirred at room temperature for 16 h. The mixture was cooled to 0 °C, quenched with 50 mL of ice cold 10% NaOH (added dropwise), and stirred vigorously for an additional 30 min. The layers were separated and the aqueous phase was extracted with two 50-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to a pale yellow oil. The oil was distilled under reduced pressure (52–55 °C at 4 mmHg, lit.[8] 47.5–48 °C at 3 mmHg) to afford 1.41 g (70.5%) of a clear, colorless liquid.

(2-Hydroxyethyl)spiropentane (5) from 2-(Methylenecyclopropyl)ethanol (6). A solution of alcohol 6 (2.15 g, 22.4 mmol) and diiodomethane (7.24 g, 26.9 mmol) in 35 mL of CH_2Cl_2 was cooled to 0 °C under a nitrogen atmosphere. A 2.0 M hexane solution of trimethylaluminum (23.6 mL, 47.1 mmol) was added in the same manner as described above and the reaction mixture was stirred at room temperature for 16 h. The workup proceeded as previously described to afford the desired product (1.77 g) in 72.2% yield: ^1H NMR ($CDCl_3$, 60 MHz) δ 3.68 (t, 2H, J = 6.8), 2.25 (variable shift, s, 1H, exchangeable with D_2O), 1.60 (m, 1H), 1.02 (m, 1H), 0.76 (m, 4H), 0.48 (t, 1H, J = 4.0); IR (neat) 3300 (br), 3063.7, 2989.5, 1046.3 cm^{-1}.

Spiropentaneacetic Acid (2). A solution of alcohol 5 (1.20 g, 10.7 mmol) in 15 mL of CH_2Cl_2 was cooled to 0 °C. The rapidly stirring solution was treated with 6.9 mL of 0.016 M (in CH_2Cl_2) of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO), 1.5 mL 0.75 M KBr, and 0.22 g of Aliquat 336 (phase-transfer catalyst). Aqueous sodium hypochlorite (0.40 M, 67 mL) was brought to pH 9 with sodium bicarbonate and added dropwise through the addition funnel so as to maintain an internal temperature below 15 °C. After the addition of the bleach, the biphasic reaction was vigorously stirred for an additional 10 min at room temperature. The pH of the mixture was adjusted to >12 with 10% NaOH. The layers were separated and the organic phase was extracted with an additional 20 mL of 10% NaOH. The combined aqueous phases were acidified to pH <2 with 6 M HCl and the product was reextracted into two 50-mL portions of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 1.24 g (92%) of a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 10.95 (br s, 1H), 2.38 (m, 2H), 1.40 (m, 1H), 1.06 (m, 1H), 0.70 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.54, 37.58, 14.48, 13.03, 12.04, 6.11, 3.48; IR (neat) 3300–2600 (br), 3062.8, 1712.7, 1302.8, 1231.5 cm^{-1}.

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