DOI 10.5012/bkcs.2010.31.6.1732

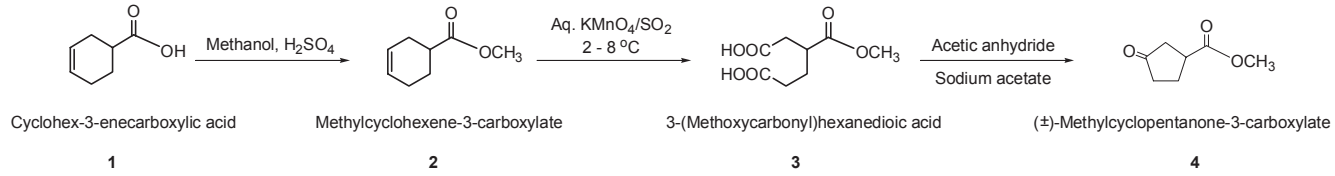
A Simple and Convenient Synthesis of (±)-Methylcyclopentanone-3-carboxylate; an Important Precursor of Antitumor Drug Sarkomycin

L. Srinivasula Reddy, N. C. Gangi Reddy,[†] T. Ram Reddy, Y. Lingappa, K. S. V. Krishna Rao,[†,‡] A. G. Damu,[†] and Yong-Ill Lee[‡,*]

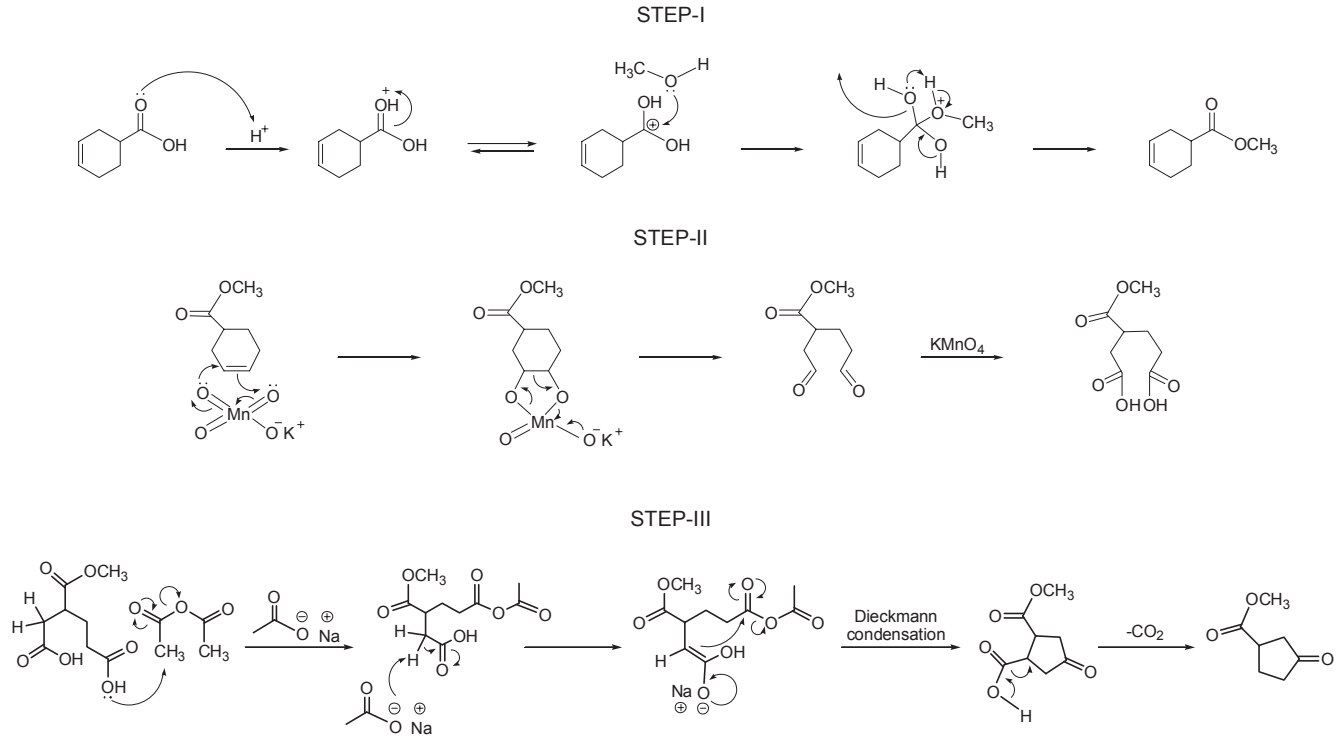
Department of Chemistry, S. V. University, Tirupati, India
[†]Department of Chemistry, Yogi Vemana University, Kadapa, India
[‡]Department of Chemistry, Changwon National University, Changwon 641-773, Korea. [*]E-mail: yilee@changwon.ac.kr
Received September 14, 2009, Accepted March 30, 2010

Key Words: Esterification, Ring opening by oxidation, Dieckmann condensation

Umezawa *et al.*[1] isolated the natural product sarkomycin, a cyclopentanoid antibiotic from the soil microorganism, *Streptomyces erythrochromogenes* in 1953. Until 1960's, sarkomycin has been used as a prescription drug against cancer in Russia, Japan and USA[2] due to its strong inhibitory effect on several human tumors including Yoshida sarcoma, Sarcoma-180 and Hela carcinoma. But its total synthesis presents great difficulties due to the fact that sarkomycin and its derivatives with five membered ring are less chemically stable, highly sensitive to both bases and acids, and undergo dimerization and polymerization easily. Owing to the increasing appearance of cyclopentane rings in large number of natural products especially those of biological importance, a great effort has recently been extended to develop new synthetic methods for the construction



Scheme 1. The simple route for the synthesis of (±)-methyl cyclopentanone-3-carboxylate



Scheme 2. The formation of cyclopentanone ring from cyclohex-3-ene system by ring opening and ring closing processes

of five-membered ring *via* three carbon annulation and Diels-Alder reaction,[3] three carbon annulation and regiospecific γ-alkylation,[4] regioselective chlorocarbonylation,[5] chemo enzymatic synthesis,[6] stereocontrolled ring opening[7] and organo catalytic hydrogenation.[8] Unfortunately, all these processes have the disadvantage of low overall yields due to a large number of individual steps and are only suitable for small scale preparations employing exotic chemicals and highly sophisticated experimental procedures.

To solve these problems, we decided to find a suitable method for the synthesis of cyclopentanoid structure, an important precursor of sarkomycin. As a result, we wish to report herein the successful accomplishment of the formation of (±)-methyl cyclopentanone-3-carboxylate (**4**) by a highly versatile three stage process starting from cyclohex-3-enecarboxylic acid (**1**) in good overall yields *via* Dieckmann condensation as the key step (Scheme 1).

We started the synthesis with esterification of cyclohex-3-ene carboxylic acid (**1**) using methanol in the presence of sulphuric acid, which afforded methylcyclohexene-3-carboxylate (**2**) with 90% yield. 3-(Methoxycarbonyl)hexanedioic acid (**3**) was obtained by oxidation of methylcyclohexene-3-carboxylate (**2**) with excess of potassium permanganate with 86% yield. Reaction of 3-(methoxycarbonyl)hexanedioic acid (**3**) with sodium acetate and acetic anhydride involving Dieckmann condensation provided (±)-methylcyclopentanone-3-carboxylate (**4**) with 84% yield. Physical and spectral data of (±)-methylcyclopentanone-3-carboxylate coincided well with those of the reported one in the literature.[5] The formation of cyclopentanone ring from cyclohex-3-ene system by ring opening and ring closing processes can be explained according to the mechanism described in Scheme 2.

In summary, we have developed a convenient approach for the preparation of (±)-methylcyclopentanone-3-carboxylate (**4**) involving simple reaction procedures and good yields, which allows the rapid access to substituted 3-oxocyclopentane carboxylicacid analogues. It could be used as convenient sarkomycin precursors and also several cyclopentanoids of pharmacological importance. We are in the way to synthesize the biologically important sarkomycin derivatives using (±)-methylcyclopentanone-3-carboxylate (**4**) as a convenient precursor.

Experimental Section

General procedure for preparation of methylcyclohexene-3-carboxylate (2). To a stirred solution of cyclohexene-3-carboxylicacid (**1**) (10.0 g, 0.0793 moles) in methanol (100 mL, 2.47 moles), added concentrated sulphuric acid and refluxed for overnight. The reaction progress was monitored by TLC. After completion of the reaction, distilled off 50 mL of methanol and the organic layer was diluted with DCM. The organic layer was washed with water followed by saturated $NaHCO_3$ solution, dried over sodium sulphate and concentrated under vacuum to obtain methylcyclohexene-3-carboxylate (**2**) and purified by column chromatography (Silica gel, Ethyl acetate and pet ether in 3:1 ratio) to get pure pale brown coloured liquid (10.0 g, 90%). bp 183 - 186 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75-1.61 (m, 2H), 2.13-1.95 (m, 2H), 2.27 (m, 2H), 2.63-2.5 (m, 1H), 3.69 (s, 3H), 5.69 (m, 2H); FT-IR (KBr, cm^{-1}): 1653; 1737; 1166; MS (EI, 70 eV): 140 (M^{+}). Anal. Calcd for: $C_8H_{12}O_2$; C, 68.54; H, 8.63; O, 22.83; Found C, 68.52; H, 8.61; O, 22.83.

3-(Methoxycarbonyl)hexanedioic acid (3). To a vigorously stirred solution of potassium permanganate (22.4 g, 0.142 moles) in 50 mL water was added methyl cyclohexene-3-carboxylate (**2**) (9.5 g, 0.068 moles) at 2 - 8 ^oC and stirred for 5 - 8 hrs at the same temperature. The reaction progress was monitored by TLC. After completion of the reaction, the excess potassium permanganate in the reaction mass was quenched by passing SO_2. Then the reaction mixture was acidified with conc. HCl and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, concentrated under reduced pressure and purified by column chromatography (Silica gel, Ethyl acetate and *n*-Hexane in 3:1 ratio) to get pure solid 3-(methoxycarbonyl)hexanedioic acid (**3**) (12 g, 86%). mp 93 - 97 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 1.75-1.65 (m, 2H), 2.56-2.18 (m, 4H), 2.73-2.67 (m, 1H), 3.59 (s, 3H), 12.3 (s, 2H); FT-IR (KBr, cm^{-1}): 3620-3470 (br); 1745; 1161; MS (EI, 70 eV): 204 (M^{+}). Anal. Calcd for: $C_8H_{12}O_6$; C, 47.06; H, 5.92; O, 47.02; Found C, 47.04; H, 5.90; O, 47.01.

(±)-Methylcyclopentanone-3-carboxylate (4). To a stirred solution of 3-(methoxycarbonyl)hexanedioic acid (**3**) (11.5 g, 0.0562 moles) in acetic anhydride (33.0 mL, 0.35 moles), added sodium acetate (8.78 g, 0.107 moles) and refluxed until the complete evolution of CO_2 gas from the reaction mass. Then the reaction mixture was stirred for overnight at 0 - 5 ^oC. The reaction progress was monitored by TLC. After completion of the reaction, the filtrate was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under reduced pressure at below 50 ^oC and purified by column chromatography by eluting with 8% ethyl acetate in pet ether to obtain pure liquid (±)-methylcyclopentanone-3-carboxylate (**4**) (6.70 g, 84%). bp 121 - 124 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00-2.58 (br m, 6H), 3.15 (quintet, 1H), 3.72 (s, 3H); FT-IR (KBr, cm^{-1}): 1735; 1697; 1282; MS (EI, 70 eV), 142 (M^{+}). Anal. Calcd for: $C_7H_{10}O_3$ C, 59.14; H, 7.09; O, 33.77; Found C, 59.12; H, 7.09; O, 33.77.

Acknowledgments. This work was supported by Priority Research Centers Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF 2009-0094066).

References and Notes

1. About the first isolation of sarkomycin from its natural source, see: (a) Umezawa, H.; Takeuchi, T.; Nitta, K.; Yamamoto, T.; Yamaoka, S. *J. Antibiot. Ser. A* **1953**, *6*, 101. (b) Umezawa, H.; Takeuchi, T.; Nitta, K.; Okami, T.; Yamamoto, T.; Yamaoka, S. *J. Antibiot. Ser. A* **1953**, *6*, 147. About sarkomycin structure elucidation, see: (c) Hoorper, Y. R.; Cheney, L. C.; Cron, M. J.; Fardig, O. B.; Johnson, D. A.; Johnson, D. L.; Palermiti, F. M.; Schmitz, H.; Wheatley, W. B. *Antibiot. Chemother.* **1955**, *5*, 585. (d) Sato, Y.; Nishioka, S.; Yonemitsu, O.; Ban, Y. *Chem. Pharm. Bull.* **1963**, *11*, 829. (e) Hill, R. K.; Foley, P. J., Jr.; Gardella, L. A. *J. Org. Chem.* **1967**, *32*, 2330.

2. (a) Umezawa, H.; Yamamoto, T.; Takeuchi, T.; Osato, T.; Okami, Y.; Yamaoka, S.; Okuda, T.; Nitta, K.; Yagishita, K.; Utahara, R.; Umezawa, S. *Antibiot. Chemother.* **1954**, *4*, 514. (b) Magill, G. B.; Golbey, R. B.; Karnofsky, D. A.; Burchenal, J. H.; Stock, C. C.; Rhodes, C. P.; Crandall, C. E.; Yorukoglu, S. N.; Gellhorn, A. *Cancer Res.* **1956**, *16*, 960. (c) Ishiyama, S. *J. Antibiot. Ser. A* **1954**, *7*, 82. (d) Goto, S.; Amano, H. *Chyrio* **1956**, *38*, 72. (e) Bickis, Y. J.; Creaser, E. H.; Quastel, J. H.; Sholefield, P. G. *Nature* **1957**, *180*, 1109. (f) Sung, S. C.; Quastel, J. H. *Cancer Res.* **1963**, *23*, 1549.
3. Jung, M. E.; Hudspeth, J. P. *J. Am.Chem. Soc.* **1977**, *99*, 5508.
4. Kodpinid, M.; Siwapinyoyos, T.; Thebtaranonth, Y. *J. Am. Chem. Soc.* **1984**, *106*, 4862.
5. Bashir-Hashemi, A.; Hardee, J. R.; Gelber, N.; Qi, L.; Axenrod, T. *J. Org. Chem.* **1994**, *59*, 2132.
6. Andrau, L.; Lebreton, J.; Viazzo, P.; Alphand, V.; Furstoss, R. *Tetrahedron Letters* **1997**, *38*, 825.
7. Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Osuna, S. O.; Maroto, B. L. *Tetrahedron Letters* **2001**, *42*, 7795.
8. Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.