# A New Regioselective Synthesis of Vicinal Bromohydrins via Free Radical Decarboxylative Bromination of β-Hydroxycarboxylic Acids

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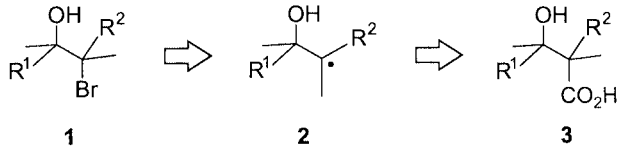
**Abstract:** Diisopropylcarbodiimide-mediated condensations between *N*-hydroxypyridine-2(1*H*)-thione and β-hydroxycarboxylic acids afforded mixed anhydrides which were regioselectively converted into vicinal bromohydrins under neutral conditions.

**Key words:** 1,2-bromohydrin, bromination, carbon radical, pyridinethione, stereoselective synthesis

Terpene- or acetogenine-derived 1,2-bromohydrins have been purified from several marine organisms.[1,2] The biological role of such secondary metabolites is subject of ongoing research.[3,4] From a synthetic point of view, it is known that vicinal bromohydrins serve as alkylating reagents[5] and are synthetically useful intermediates in a variety of selective transformations.[6] In view of this background, efficient and reliable syntheses of β-bromohydrins[7] have been developed which predominantly start from olefins,[8] epoxides,[9] or diols.[10] Surprisingly, nothing has been reported so far on the synthesis of 2-bromoalcohols using free radical-based methods.[11] The latter type of transformations may be performed under mild and neutral conditions thus offering advantages for regioselectively preparing unsaturated β-bromohydrines without competing electrophile-induced side reactions. In order to pursue a project which requires the availability of pure 2-bromoalkenols in sufficient quantities, we have addressed the synthetic problem of converting 2-hydroxycarboxylic acids **3** via intermediate alkyl radicals **2** into 2-bromoalcohols **1** (Figure 1). We disclose our results in the present communication.[11,12]




1 2 3

**Figure 1** Starting material **3** and reactive intermediates **2** in a new synthesis of β-bromohydrins **1** under neutral conditions. $R^1$, $R^2$ = H, alkyl, phenyl.

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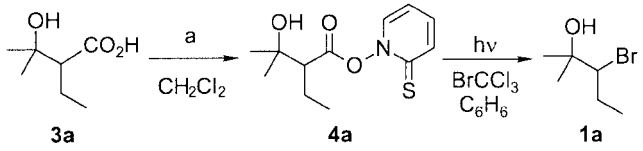
2-Ethyl-3-methyl-3-hydroxybutyric acid (**3a**) was selected as starting material in order to establish a synthetically useful radical-based route to 3-bromo-2-methyl-2-pentanol (**1a**) (trapping of a secondary radical in vicinity of a tertiary hydroxyl group, Table 1). For this purpose, a solution of *N*-hydroxypyridine-2(1*H*)-thione[13] (not shown in Table 1) and β-hydroxycarboxylic acid **3a** in anhydrous $CH_2Cl_2$ was treated for 20 hours at 20 °C with diisopropylcarbodiimide (DIC) to furnish *N*-acyloxy-substituted pyridinethione **4a** in approximately 70% yield. No transformation was seen if *N*-hydroxypyridine-2(1*H*)-thione was stirred in the presence DIC in a solution of $CH_2Cl_2$ alone. In the absence of *N*-hydroxypyridine-2(1*H*)-thione, substrate **3a** was almost quantitatively converted by DIC into 2-ethyl-3,3-dimethyl-β-propiolactone[14] (81%, if purified by column chromatography) – a product that was not observed in the original reaction mixture, from which target product **4a** had been obtained. Treatment of this β-lactone for 20 hours in $CH_2Cl_2$ with *N*-hydroxypyridine-2(1*H*)-thione furnished 10% of thione **4a** (NMR). Approximately 60% of β-lactone was recovered from this experiment.

Radical precursor **4a** was identified by its characteristic $^{13}C$ NMR signals, especially those originating from the pyridinethione entity [e.g. δ = 175.4 (C=S) and 113.1 (C4)].[15] This compound was stable, if stirred for 20 hours at 20 °C in the dark ($^1H$ NMR) but it decomposed to a considerable degree when subjected to column chromatography. Therefore, crude **4a**, as obtained after work up using extractions only, was dissolved in $C_6H_6$ and photolyzed in the presence of $BrCCl_3$ to furnish target compound **1a** in ca 75% yield (50% from **3a**).[16,17] No attempts were made to apply alternative bromine atom donors for this purpose since this issue had been addressed previously.[18] Addition of DMAP in order to facilitate the anhydride forming step did not improve the overall yield of bromohydrin **1a** from hydroxyacid **3a** (Table 1, entries 1 and 2). It should be added that this modification was in other instances useful in order to raise the yields of alkyl radical precursors by ca 5–10% thus improving the overall efficiency of the new bromohydrin synthesis (see Schemes 1 and 3). A change to dicyclohexylcarbodiimide (DCC) as dehydrating reagent provided comparable results to DIC (Table 1, entry 3).[19] In view of the fact that *N*,*N*′-diisopropyl urea was frequently easier to remove on a quantitative scale from the reaction mixtures, we adhered to the use of DIC as standard reagent. An

application of trispropanephosphonic acid anhydride for this purpose completely failed.[20] Likewise, attempts to convert *N*-hydroxy-4-methyl-5-(*p*-anisyl)thiazole-2(3*H*)-thione[21] (not shown) into the corresponding *N*-acyloxy derivative, according to the conditions which are outlined in Table 1, were not successful for reasons which have yet to be explored.

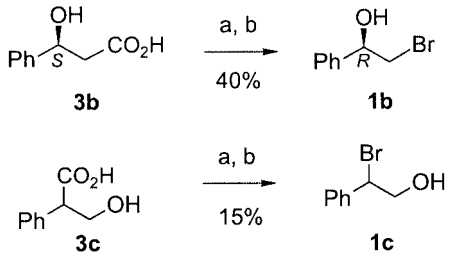
**Table 1** The Synthesis of 3-Bromo-2-methyl-2-pentanol (**1a**) from 2-Ethyl-3-methyl-3-hydroxybutyric Acid (**3a**)




**3a** **4a** **1a**

| Entry | Conditions[a] | **1a** Yield (%) |
|---|---|---|
| 1 | DIC | 50 |
| 2 | DIC/DMAP | 48 |
| 3 | DCC/DMAP | 51 |

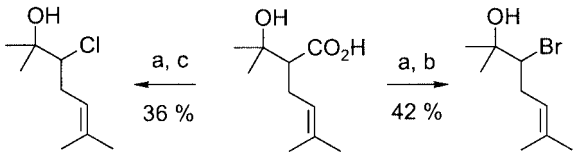
The new method was applied for the synthesis of enantiomerically pure (*R*)-2-bromo-1-phenyl-1-ethanol (**1b**) {$[\alpha]_D^{20}$ = –40.8 (*c* 1.01, $CH_2Cl_2$)}[22] from (*S*)-configured acid **3b** (> 98% ee; trapping of a primary radical in vicinity of a benzylic hydroxyl group, Scheme 1). Although the yield of this two step sequence could not compete with the synthesis of bromohydrin **1b** from styrene via HOBr addition,[23] it represents one of the rare examples that proceeds with complete regioselectivity and a full conservation of stereointegrity at C1.[24] The synthesis of 2-bromo-2-phenylethanol (**1c**) was unfortunately associated with a poor yield (trapping of a benzylic radical in vicinity of a primary hydroxyl group). Complications in the latter reaction arose especially in the initial step (not shown in Scheme 1) which provided significant amounts of yet unidentified products besides the desired *N*-acyloxypyridine-2(1*H*)-thione.




**3b** **1b** **3c** **1c**

**Scheme 1** Regioselective synthesis of styrene-derived β-bromohydrins **1b** and **1c**. Reagents and conditions: (a) *N*-hydroxypyridine-2(1*H*)-thione, DIC, DMAP, $CH_2Cl_2$, 20 °C; (b) $BrCCl_3$, $C_6H_6$, 20 °C, hν.

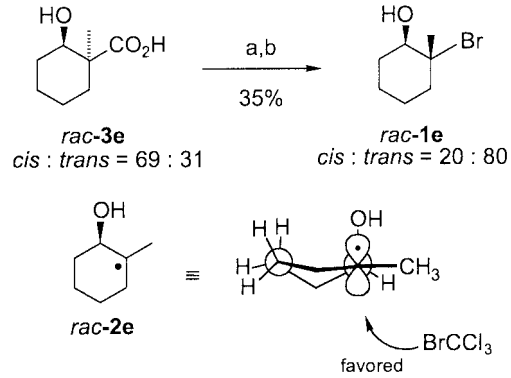
δ-Unsaturated β-bromohydrin **1d** (42%, $BrCCl_3$ as trapping reagent) and the corresponding chlorohydrin **5** (36%, $CCl_4$ as chlorine atom donor) were prepared on a synthetic scale starting from 2-(1-methyl-1-hydroxyethyl-5-methylhexenoic acid (**3d**) (Scheme 2). No spectroscopic evidence for the formation of side products originating from competing ring closure reactions were observed in both instances ($^1$H NMR).




**5** **3d** **1d**

**Scheme 2** Formation of unsaturated 2,3-halohydrins **1d** and **5**. Reagents and conditions: (a) *N*-hydroxypyridine-2(1*H*)-thione, DIC, $CH_2Cl_2$, 20 °C; (b) $BrCCl_3$, $C_6H_6$, 20 °C, hν; (c) $CCl_4$, $C_6H_6$, 20 °C, hν.

The conversion of 2-hydroxy-1-methylcyclohexylcarboxylic acid **3e** into cyclic β-bromohydrin *rac*-**1e** (*cis*:*trans* = 20:80, trapping of a tertiary radical in vicinity of a secondary hydroxyl group) was feasible although the yields remained moderate. The relative *trans*-configuration of the major diastereomer of **1e** was verified by an independent synthesis of this compound. Treatment of 1-methylcyclohexene oxide under stereocontrolled conditions using $MgBr_2 \cdot Et_2O$ in $Et_2O$ (T = 20 °C)[25] and subsequent hydrolysis of the reaction mixture using an aqueous phosphate buffer provided 83% of a 56:44 mixture of *trans*-**1e** and *trans*-2-bromo-1-methylcyclohexanol (not shown), i.e. the product of HOBr-addition to 1-methylcyclohexene.[26] The observed stereoselectivity in the radical-based bromohydrin synthesis is explicable via selective bromine atom delivery that occurs for steric reason preferentially from the opposite side of the hydroxyl substituent, which affords *trans*-**1e** as major bromoalcohol (Scheme 3).[27]




**Scheme 3** Stereoselective synthesis of *trans*-2-bromo-2-methylcyclohexanol (*trans*-**3e**) from hydroxycarboxylic acid **1e**. Reagents and conditions: (a) *N*-hydroxypyridine-2(1*H*)-thione, DIC, DMAP, $CH_2Cl_2$, 20 °C; (b) $BrCCl_3$, $C_6H_6$, 20 °C, hν.

In conclusion, we have demonstrated the feasibility, scope, and limitation of β-bromohydrin formation under neutral, i.e. non-oxidative conditions, starting from β-hydroxycarboxylic acids. The reaction is considered to offer advantages for syntheses of unsaturated β-bromo- or β-chlorohydrins, where polar methods lead to complications such as a partial racemization or rearrangements.

**Experimental Section**

A solution of 2-ethyl-3-hydroxy-3-methylbutyric acid (**3a**) (439 mg, 3.0 mmol) and *N*-hydroxypyridine-2(1*H*)-thione (401 mg, 3.15 mmol) in anhyd $CH_2Cl_2$ (8 mL) was treated at 0 °C dropwise (within 20 min) with a solution of DIC (416 mg, 3.30 mmol) in anhyd $CH_2Cl_2$ (7 mL) in the dark. Stirring was continued for 2 h at 0 °C and for 20 h at 20 °C in the dark. Afterwards the volatiles were removed under reduced pressure to provide a crude product that was taken up in $Et_2O$. The precipitate was removed by filtration. The solids were washed with $Et_2O$. Combined filtrate and washings were concentrated under reduced pressure to furnish pyridinethione **4a** as brown oil: 856 mg (**4a**: 70% yield, $^1$H NMR). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.3 Hz), 1.36 (s, 3 H), 1.40 (s, 3 H), 1.65–1.95 (m, 2 H), 2.77 (dd, *J* = 11.8, 3.3 Hz, 1 H), 6.68 (dt, *J* = 7.0, 1.8 Hz, 1 H), 7.23 (ddd, *J* = 8.8, 7.0, 1.3 Hz, 1 H), 7.52 (dd, *J* = 7.0, 1.3 Hz, 1 H), 7.71 (dd, *J* = 8.8, 1.8 Hz, 1 H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ = 12.9, 21.7, 25.3, 29.3, 58.2, 72.0, 113.1, 133.8, 137.2, 137.9, 169.8, 175.4. A flask was charged with crude **4a**, $BrCCl_3$ (2.38 g, 12.0 mmol) and $C_6H_6$ (20 mL). The solution was deaerated in 3 freeze-pump-thaw-cycles (Ar as flushing gas) and was photolyzed at 20 °C for 30 min using incandescent light (250 W). The volatiles were removed under reduced pressure to furnish an oil which was purified by Kugelrohr distillation (120–140 °C, 50 mbar) to provide 271 mg (50%) of 3-bromo-2-methyl-2-pentanol (**1a**) as colorless oil. $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.3 Hz, 3 H), 1.32 (s, 3 H), 1.36 (s, 3 H), 1.73 (ddq, *J* = 14.2, 11.3, 7.3 Hz, 1 H), 1.94 (ddq, *J* = 14.2, 2.1, 7.3 Hz, 1 H), 2.23 (s, 1 H, OH), 3.98 (dd, *J* = 11.3, 2.1 Hz, 1 H). $^{13}$C NMR (63 MHz, $CDCl_3$): δ = 13.7, 25.7, 26.8, 27.3, 72.5, 74.2. IR (neat): 3405 (s), 2974 (s), 2878 (s), 1704 (s), 1462 (m), 1380 (s), 1165 (s), 1132 (s), 806 (s), 624 (s) cm$^{-1}$. MS (70 eV, EI): *m*/*z* = 165 (2) [$M^+ - CH_3$], 100 (4) [$M^+$ – HBr], 83 (4) [$M^+$ – HOBr], 59 (100) [$C_4H_{11}^+$], 43 (28) [$C_3H_7^+$]. Anal. Calcd for $C_6H_{13}BrO$ (181.1): C, 39.80; H, 7.24. Found: C, 40.65; H, 7.21.

**3-Bromo-2,6-dimethyl-5-hepten-2-ol** (**1d**): Purified by column chromatography ($SiO_2$, petroleum ether–*tert*-butyl methyl ether, 5:1, $R_f$ = 0.42). $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.38 (s, 3 H), 1.63 (s, 3 H), 1.74 (d, *J* = 1.2 Hz, 3 H), 2.01 (s, 1 H, OH), 2.40–2.54 (m, 1 H, 4-H), 2.60–2.71 (m, 1 H), 4.02 (dd, *J* = 10.7, 2.9 Hz, 1 H), 5.22 ($m_c$, 1 H). $^{13}$C NMR (63 MHz, $CDCl_3$): δ = 18.1, 25.7, 25.8, 26.8, 32.9, 71.2, 72.5, 121.6, 134.1. IR (neat): 3423 (s), 2974 (s), 2925 (m), 1450 (w), 1378 (m), 1258 (w), 1114 (w), 833 (w), 785 (w) cm$^{-1}$. MS (70 eV, EI): *m*/*z* (%) = 123 (63) [$M^+$ – HOBr], 69 (96) [$C_5H_9^+$], 59 (96) [$C_3H_6O^+$], 41 (100) [$C_3H_5^+$]. Anal. Calcd for $C_9H_{17}BrO$ (221.1): C, 48.88; H, 7.75. Found: C, 48.74; H, 7.88.

**3-Chloro-2,6-dimethyl-5-hepten-2-ol** (**5**): Purified by column chromatography ($SiO_2$, petroleum ether–*tert*-butyl methyl ether, 5:1, $R_f$ = 0.44). $^1$H NMR (250 MHz $CDCl_3$): δ = 1.31 (s, 3 H), 1.33 (s, 3 H), 1.63 (s, 3 H), 1.74 (d, *J* = 0.9 Hz, 3 H), 2.06 (s, 1 H, OH), 2.26–2.39 (m, 1 H), 2.51–2.63 (m, 1 H), 4.02 (dd, *J* = 10.7, 2.8 Hz, 1 H), 5.23 (m, 1 H). $^{13}$C NMR (63 MHz, $CDCl_3$): = 18.0, 25.2, 25.8, 26.5, 32.0, 72.8, 74.3, 120.8, 134.2. IR (neat): 3409 (s), 2979 (s), 2912 (m), 2871 (w), 1447 (m), 1381 (s), 1259 (m), 937 (m), 682 (m) cm$^{-1}$. MS (70 eV, EI): *m*/*z* (%) = 140 (6) [$M^+$ – HCl], 123 (33) [$C_5H_{10}OCl^+$], 69 (47) [$C_5H_9^+$], 59 (100) [$C_3H_7O^+$], 41 (40) [$C_3H_6^+$]. HRMS: *m*/*z* [$M^+$ – HCl] calcd for $C_9H_{16}O$: 140.1201; found: 140.1202.

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## References

(1) (a) Blunt, J. W.; Cropp, B. R.; Munro Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2003**, *20*, 1. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1.
(2) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937.
(3) Neidleman, S. L.; Geigert, J. *Biohalogenations: Principles, Basic Roles and Applications*; Ellis Horwood Limited: Chichester, **1986**, 112.
(4) Fukuzawa, A.; Aye, M.; Takasugi, Y.; Nakamura, M.; Tamura, M.; Murai, A. *Chem. Lett.* **1994**, 2307.
(5) (a) Espinosa, E.; Belmant, C.; Pont, F.; Luciani, B.; Poupot, R.; Romagné, F.; Brailly, H.; Bonneville, M.; Fournie, J.-J. *J. Biol. Chem.* **2001**, *276*, 18337. (b) Song, Q.; Negrete, G. R.; Wolfe, A. R.; Wang, K.; Meehan, T. *Chem. Res. Toxicol.* **1998**, *11*, 1057.
(6) (a) Blaser, A.; Reymond, J.-L. *Synlett* **2000**, 817. (b) Nandanan, E.; Phukan, P.; Sudalai, A. *Indian J. Chem., Sect. B* **1999**, *38*, 283.
(7) For reviews see: (a) Bonini, C.; Righi, G. *Synthesis* **1994**, 225. (b) Boguslavskaya, L. S. *Russ. Chem. Rev.* **1972**, *41*, 740.
(8) (a) Raghavan, S.; Reddy, S. R.; Tony, K. A.; Kumar, C. N.; Varma, A. K.; Nangia, A. *J. Org. Chem.* **2002**, *67*, 5838. (b) Bailey, P. L.; Briggs, A. D.; Jackson, R. F. W.; Pietruszka, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3359. (c) Conte, V.; Di Furia, F.; Moro, S. *Tetrahedron Lett.* **1996**, *37*, 8609. (d) Roedig, A. In *Houben–Weyl, Methoden der organischen Chemie*, 4th ed., Vol. 5/4; Müller, E., Ed.; Thieme: Stuttgart, **1960**, 133.
(9) (a) Sharghi, H.; Niknam, K.; Pooyan, M. *Tetrahedron* **2001**, *57*, 6057. (b) Afonoso, C. A. M.; Vieira, N. M. L.; Motherwell, W. B. *Synlett* **2000**, 382. (c) Shargi, H.; Naeimi, H. *J. Chem. Res., Synop.* **1999**, 310. (d) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1992**, *48*, 3805. (e) Alvarez, E.; Nuñez, M. T.; Martín, V. S. *J. Org. Chem.* **1990**, *55*, 3429.
(10) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.
(11) For related transformations see: (a) Formation of bromhydrin ethers: Hamdani, M.; De Jeso, B.; Deleuze, H.; Maillard, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1229. (b) Reductive decarboxylation: Socha, D.; Jurczak, M.; Chmielewski, M. *Carbohydr. Res.* **2001**, *336*, 315.
(12) $Pb(OAc)_4$-mediated oxidations of β-hydroxycarboxylic acids furnish substituted epoxides: Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 1965.
(13) Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317.
(14) Wedler, C.; Kleiner, K.; Kunath, A.; Schick, H. *Liebigs Ann.* **1996**, 881.
(15) Hartung, J.; Hiller, M.; Schwarz, M.; Svoboda, I.; Fuess, H. *Liebigs Ann.* **1996**, 2091.
(16) For the original work on the use of $BrCCl_3$ in the free radical-based decarboxylative bromination of carboxylic acids see: Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(17) For a comprehensive review on free radical-based transformations of *N*-acyloxypyridine-2(1*H*)-thiones see: Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.
(18) Hartung, J.; Kneuer, R.; Laug, S.; Schmidt, P.; Špehar, K.; Svoboda, I.; Fuess, H. *Eur. J. Org. Chem.* **2003**, 4033.
(19) For alternative syntheses of *N*-acyloxypyridine-2(1*H*)-thiones see: Motherwell, W. B.; Imboden, C. In *Radicals in Organic Synthesis*, Vol. 1; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**, 109.

(20) (a) Wissmann, H.; Kleiner, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 134. (b) Hartung, J.; Schwarz, M. *Synlett* **2000**, 371.
(21) Hartung, J.; Gottwald, T.; Špehar, K. *Synlett* **2003**, 227.
(22) Imuta, M.; Kawai, K.-I.; Ziffer, H. *J. Org. Chem.* **1980**, *45*, 3352.
(23) Andersson, M.; Conte, V.; Di Furia, F.; Moro, S. *Tetrahedron Lett.* **1995**, *36*, 2675.
(24) Iranpoor, N.; Kazemi, F.; Salehi, P. *Synth. Commun.* **1997**, *27*, 1247.
(25) Lupatelli, P.; Bonini, C.; Caruso, L.; Gambacorta, A. *J. Org. Chem.* **2003**, *68*, 3360.
(26) Porter, D. J.; Stewart, A. T.; Wigal, C. T. *J. Chem. Educ.* **1995**, *72*, 1039.
(27) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067.