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# Enantioselective Synthesis of (R)-(–)-2,6-Dimethyl Heptanoic Acid: The First Application of the DITOX Asymmetric Building Block

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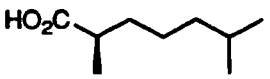
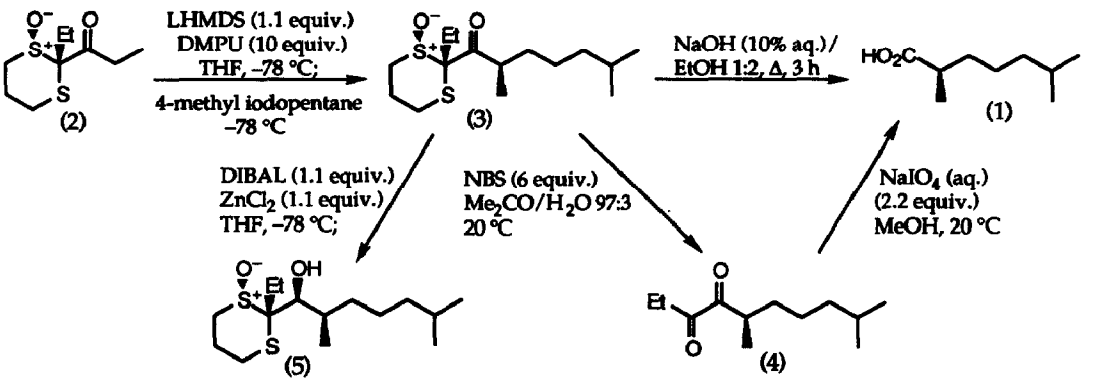
***Abstract:*** The 1,3-dithiane 1-oxide (DITOX) asymmetric building block/chiral auxiliary has been used to prepare (*R*)-(–)-2,6-dimethyl heptanoic acid (1), a simple derivative of citronellal, in two steps from (2).

Simple 1,3-dithiane 1-oxide (DITOX) derivatives can act as combined chiral auxiliaries and asymmetric building blocks for the enantiocontrol of a wide range of organic reactions. For example we have shown that 2-acyl-2-alkyl-1,3-dithiane 1-oxides undergo highly diastereoselective enolate alkylation,[1] Mannich reaction,[2] carbonyl group reduction,[3] Grignard reagent addition,[4] hetero-cycloaddition,[5] and conjugate addition reactions;[6] in many cases stereoselectivity is sufficiently high that the minor isomer is not detected using 400 MHz $^1$H NMR spectroscopy. The acyl dithiane oxide building blocks are available enantioselectively in up to optical purity; they are inexpensive and of relatively low molecular weight; both enantiomers are available in all cases.[7,8] A chelation-control model of the reactivity of these systems allows us to predict with certainty the major product isomer to be formed in all the reaction types so far studied. We now report the first application of the DITOX unit to an enantioselective synthesis, that of (*R*)-(–)-2,6-dimethyl heptanoic acid (1),[9] a natural product derivative containing a carboxylic acid function substituted at the α-carbon atom, a feature common to many analgesic compounds. This simple application demonstrates for the first time all of the methodology necessary for the use of DITOX units as chiral auxiliaries, including removal.




(1)

The synthesis was completed initially in the racemic series from (±)-*anti*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxide (±)-(2). Generation of the enolate using lithium hexamethyl disilazide and treatment with 1-iodo-4-methylpentane in the presence of DMPU resulted in a very highly diastereoselective reaction to give (±)-(3) with no trace of the minor stereoisomer at the alkylated centre visible in the 400 MHz $^1$H NMR spectrum. No alkylation took place in the absence of DMPU. Cleavage to give the acid (±)-(1) was accomplished by ready hydrolysis to the diketone (±)-(4) with NBS (75%),[10] followed by oxidative cleavage using sodium periodate (60%) (Scheme).[11]




For the optically pure series, (1*R*,2*R*)-(+)-*anti*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxide, (1*R*,2*R*)-(+)-(2) ($[\alpha]_{20}^{D}$ = +280.8 °; c = 1 ($CHCl_3$)), predicted by our rule of thumb to lead to the correct absolute stereochemistry in the final product, was prepared by enantioselective sulphur oxidation of *anti*-2-ethyl-2-propanoyl-1,3-dithiane followed by crystallization to optical purity.[7] Enolate alkylation as described above led to optically pure (1*R*,2*R*,2'*R*)-(+)-(5) ($[\alpha]_{20}^{D}$ = +166.8 °; c = 1 ($CHCl_3$)) in 57% yield without complication and in an equally highly stereoselective reaction. In this case, however, conversion into acid (*R*)-(–)-(1) using the two-step procedure successful for the racemate was expected to lead to racemization through ready enolization of the diketone, and, while reduction proceeded in good yield, again with very high diastereoselectivity,[3] thus introducing two new contiguous asymmetric centres overall, the resulting alcohol (1*R*,2*R*,1'*S*,2'*R*)-(+)-(5) ($[\alpha]_{20}^{D}$ = +45.6 °; c = 1 ($CHCl_3$)) proved resistant to hydrolysis to the keto alcohol[12] Fortunately, simple base-mediated deacylation of (+)-(3), a technique also used by us[8] and others[13] to prepare non-racemic dithiane derivatives, led directly to (*R*)-(–)-(1), we believe without loss of stereochemical integrity,[14] in 39% yield ($[\alpha]_{20}^{D}$ = –18.21 °; c = 1.01 ($CHCl_3$)); (lit.: $[\alpha]_{20}^{D}$ = –17.5 °)).[15] The synthesis thus proceeds to give essentially optically pure (*R*)-(–)-(1) in two steps from (2); in addition the 2-ethyl-1,3-dithiane 1-oxide auxiliary is recoverable in optically pure form (Scheme). We hope that this simple synthesis will pave the way for further application of the DITOX asymmetric building block.

**Acknowledgment**

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**References**

1. Page, P. C. B.; Westwood, D.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 185; Page, P. C. B.; Klair, S. S.; Westwood, D. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2441.
2. Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *J. Org. Chem.*, **1993**, *58*, 6902.
3. Page, P. C. B.; Prodger, J. C. *Synlett* **1990**, 460.
4. Page, P. C. B.; Westwood, D.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1158.
5. Page, P. C. B.; Prodger, J. C. *Synlett* **1991**, 84.
6. Page, P. C. B.; Prodger, J. C.; Hursthouse, M.; Mazid, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 167.
7. Page, P. C. B.; Namwindwa, E. S.; Klair, S. S.; Westwood, D. *Synlett* **1990**, 457.
8. Page, P. C. B.; Namwindwa, E. S., *Synlett* **1991**, 80; Page, P. C. B.; Gareh, M. T.; Porter, R. A. *Tetrahedron: Asymmetry* **1993**, 2139.
9. von Braun, J.; Teuffert, W; Manz, G. *Ber.*, **1929**, *62*, 235; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1954**, *37*, 881.
10. Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
11. Shiner, V. J.; Wasmuth, C. W. *J. Am. Chem. Soc.* **1959**, *81*, 37.
12. Page, P. C. B.; Graham, A. E.; Park, B. K. *Tetrahedron* **1992**, *48*, 7265.
13. Aggarwal, V. K.; Evans, G.; Moya, E.; Dowden, J. *J. Org. Chem.* **1992**, *57*, 6390.
14. Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525.
15. Kögl, F.; Boer, A. G. *Rec. Trav. Chim. Pays-Bas* **1935**, *54*, 779. These authors resolved the acid through the cinchonidine salt; in order to allow maximum reliance to be placed upon our figure the optical rotation was measured several times, each after a repurification, and at different dilutions.

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