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An efficient strategy for the synthesis of 5-hydroxyalkylbutan-4-olides from D-mannitol: total synthesis of (−)-muricatacin

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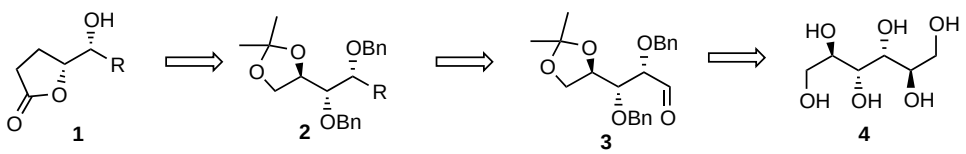
Abstract—A general approach towards the synthesis of 5-hydroxyalkylbutan-4-olides from D-mannitol has been described. The approach has successfully been used for the total synthesis of (−)-muricatacin, an anti-tumor natural product.

Chiral hydroxylactones occupy an important position as bio-active molecules and useful synthetic intermediates in total synthesis. One such group of hydroxylactones comprises the 5-hydroxyalkylbutan-4-olides **1**. These are widely found in nature and show diverse biological properties. Some of these compounds are known to have insect antifeedant activity[1] and are cytotoxic to human tumor cells.[2] The short chain homologues are important flavor constituents in wine, sherry, and tobacco smoke.[3] These are also found in microbial metabolite cultures of *Erwinia quernica*[4] and *Streptomyces griseus*.[5] Many of these butanolides are often used as synthons in the synthesis of complex and biologically important natural products.[6] These have been used as precursors to HIV-1 protease inhibitors.[7] One such molecule that has attracted much attention since its isolation was (−)-muricatacin **1d**. It was isolated from the seeds of *Anona muricata* L. (annonaceae),[8] commonly known as sour soup or guanabana, and is grown commercially as a fruit crop throughout the tropical regions of the world. This plant as well as others in the family of annonaceae are a source of many annonaceous acetogenins that are known to have anti-tumor properties.[2] Both enantiomers of **1d** are found in nature. The isolated material is a mixture of the two, the (−)-(*R*,*R*)-enantiomer **1d** being predominant (ee of ca. 25% based on optical rotation). It has been shown to be cytotoxic towards human tumor cells. Biological studies revealed that the length of the side chain is very crucial. Decreasing the length of the alkyl side chain led to decreased activity but increasing the chain length did not show any increase in activity. Both (+)- and (−)-muricatacin (*threo*) have the same activity. The biological activity of muricatacin and other related compounds has prompted many syntheses of this type of molecule.[9–11] Most of the syntheses are target oriented. In this paper we describe a general approach, which can be used for synthesizing (−)-muricatacin and related natural products.

While working on the total synthesis of (−)-boronolide[12] and hexadecanolide, a pheromone,[13] we realized that 5-hydroxyalkylbutan-4-olide **1** type natu-



a: R = CH_3; **b**: R = C_4H_9; **c**: R = C_5H_{11}
d: R = $C_{12}H_{25}$; **e**: R = CH_2CH_2Ph

Scheme 1.

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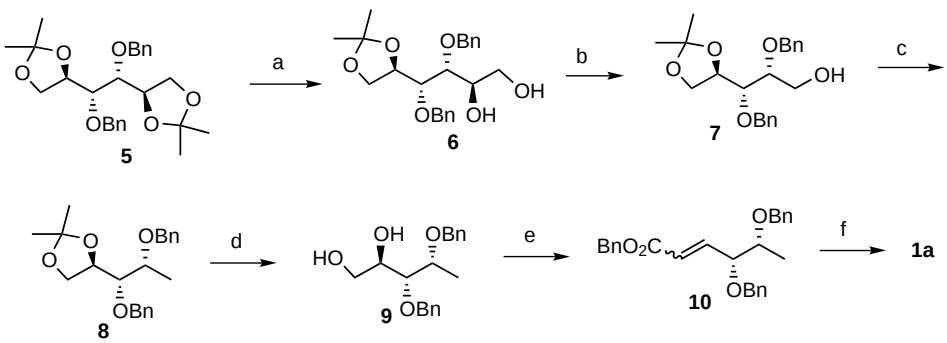
ral products can also be synthesized easily from D-mannitol. The retrosynthetic analysis for our approach is shown in Scheme 1. The γ-lactone unit can be constructed from the corresponding hydroxy acid, which can originate from the acetonide **2**. The appropriate alkyl group can be added to the aldehyde of **3**.

The synthesis commences with the diacetonide benzyl ether **5**,[14] which was subjected to selective hydrolysis using acetyl chloride in MeOH at 0°C to give diol **6** in 88% yield. The diol **6** was subjected to oxidative cleavage using lead tetraacetate (LTA) in CH_2Cl_2 and the crude aldehyde was reduced with $NaBH_4$ to provide alcohol **7**. The alcohol was then tosylated, and the crude tosylate was reduced with $NaBH_4$ in DMSO to give **8** whose acetonide group was cleaved using trifluoroacetic acid in THF–water mixture (4:1). The diol **9**, thus obtained, was cleaved to give an aldehyde using LTA as above. This aldehyde, without any purification, was subjected to a Wittig olefination reaction with (benzyloxycarbonylmethylene)triphenylphosphorane to give the α,β-unsaturated ester **10**, which was converted into the target compound **1a** by hydrogenation over Pd/C followed by treatment of the resulting crude hydroxy acid with *p*-TsOH (Scheme 2).

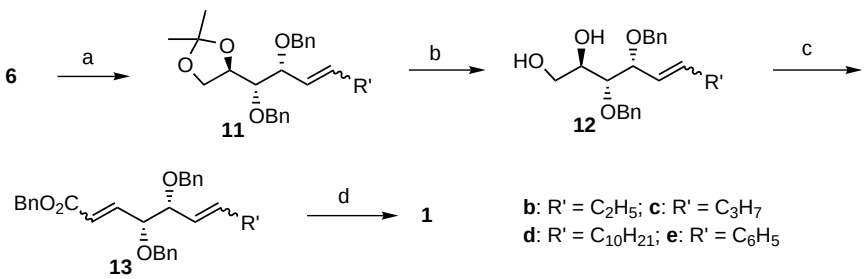
We extended this approach to compounds with different alkyl groups in the side chain. For alkyl groups other than Me, the scheme was modified. The aldehyde, obtained from the diol **6**, was treated with ylides, prepared from phosphonium salts with different alkyl groups to provide olefin **11**. The acetonide group of **11** was cleaved, as above. The diol **12**, thus obtained, was converted into the olefinic compound **13** using Wittig chemistry. Conversion of **13** into target compounds such as **1b**, **1c**, **1d**, and **1e** was carried out as for **1a**. In this way, we were able to synthesize several hydroxyalkyl γ-lactones in ~45% overall yield (Scheme 3).

In order to show more versatility in our approach, we studied the synthesis of analogues having extra hydroxyl groups. This was accomplished from the known diol **14**,[12] which was subjected to oxidative cleavage with LTA, and the aldehyde so obtained was allowed to react with an ylide prepared from (ethoxycarbonylmethylene)triphenylphosphorane to provide the α,β-unsaturated ester **15** as a mixture of *cis* and *trans* isomers (ratio 70:30). This mixture, on treatment with $CuCl_2{\cdot}2H_2O$[15] gave a lactone after cleaving the acetonide group. It is to be mentioned here that only the *cis* isomer lactonized and the *trans* isomer remained unchanged. The unsaturated lactone **16** was hydrogenated to provide the saturated lactone **17** which could be an important precursor in synthesis (Scheme 4).

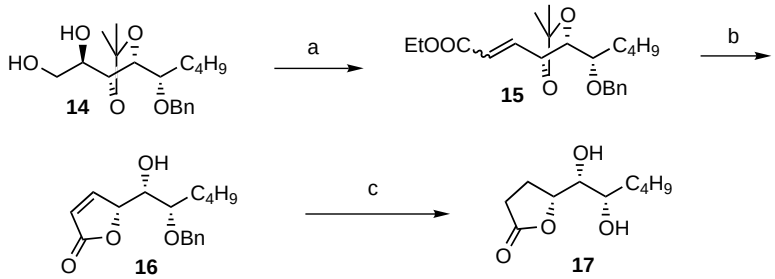
In conclusion, we have developed a simple and flexible strategy for the synthesis of hydroxyalkylbutan-4-olides from D-mannitol. Using the above strategy, a total synthesis of (–)-muricatacin **1d**[16] was accomplished.



Scheme 2. *Reagents and conditions*: (a) AcCl (5 equiv.), MeOH, 0°C, 5 min (88% yield); (b) (i) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (ii) $NaBH_4$, EtOH, 0°C, 2 h (96% yield); (c) (i) TsCl, Et_3N, CH_2Cl_2, 14 h; (ii) $NaBH_4$, DMSO, 160°C, 7 min (73% yield); (d) TFA, THF–H_2O (4:1), 65°C, 6 h (86% yield); (e) (i) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (ii) $BnO_2CCH_2P^+Ph_3Br^-$, *n*-BuLi, THF, 0°C–rt, 12 h (74% yield); (f) (i) H_2, 10% Pd/C, EtOH, rt, 12 h; (ii) *p*-TSA, toluene, 70°C, 1 h (95% yield).



Scheme 3. *Reagents and conditions*: (a) (i) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (ii) $R'CH_2P^+Ph_3Br^-$, *n*-BuLi, THF, 0°C–rt, 12 h (65–75% yield); (b) TFA, THF–H_2O (4:1), 65°C, 6 h (85–95% yield); (c) (i) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (ii) BnO_2CCH_2P+Ph_3Br-, *n*-BuLi, THF, 0°C–rt, 12 h (70–80% yield); (d) (i) H_2, 10% Pd/C, EtOH, rt, 12 h; (ii) *p*-TSA, toluene, 70°C, 1 h (92–95% yield).



Scheme 4. *Reagents and conditions*: (a) (i) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (ii) $EtO_2CCH{=}PPh_3$, MeOH, rt, 12 h (75% yield); (b) $CuCl_2{\cdot}2H_2O$, MeCN, rt, 12 h (65% yield); (c) H_2, 10% Pd/C, EtOH, rt, 12 h.

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References

1. Numata, A.; Hokimoto, K.; Takemura, T.; Katsuno, T.; Yamamoto, K. *Chem. Pharm. Bull.* **1984**, *32*, 2815.
2. Cave, A.; Chaboche, C.; Figadere, B.; Harmange, J. C.; Laurens, A.; Peyrat, J. F.; Pichon, M.; Szlosek, M.; Cotte-Lafitte, J.; Quero, A. M. *Eur. J. Med. Chem.* **1997**, *32*, 617.
3. (a) Muller, C. J.; Maggiora, L.; Kepner, R. E.; Webb, A. D. *J. Agric. Food Chem.* **1969**, *17*, 1373; (b) Muller, C. J.; Kepner, R. E.; Webb, A. D. *Am. J. Enol. Viticult.* **1973**, *24*, 5; (c) Schumacher, J. N.; Green, C. R.; Best, F. W.; Newell, M. P. *J. Agric. Food Chem.* **1977**, *25*, 310.
4. Wright, A. E.; Matthias, M.; Midland, S.; Munnecke, D. E.; Sims, J. J. *Tetrahedron Lett.* **1989**, *30*, 5699.
5. Grafe, U.; Reinhardt, G.; Schade, W.; Krebs, D.; Eritt, I.; Fleck, W. F.; Heinrich, E.; Radics, L. *J. Antibiot.* **1982**, *35*, 609.
6. (a) Matsumoto, T.; Ichihara, A.; Ito, N. *Tetrahedron* **1969**, *25*, 5889; (b) Iwaki, S.; Marumo, S.; Saito, T.; Yamada, M.; Katagiri, K. *J. Am. Chem. Soc.* **1974**, *96*, 7842; (c) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217; (d) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012; (e) Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035.
7. (a) Nishi, T.; Kataoka, M.; Morisawa, Y. *Chem. Lett.* **1989**, 1193; (b) Gante, J.; Kahlenberg, H. *Chem.-Ztg.* **1991**, *115*, 215; (c) Chakraborty, T. K.; Gangakhedkar, K. K. *Tetrahedron Lett.* **1991**, *32*, 1897; (d) Harding, K. E.; Coleman, M. T.; Liu, L. T. *Tetrahedron Lett.* **1991**, *32*, 3795; (e) Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *J. Org. Chem.* **1991**, *56*, 6500; (f) Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411; (g) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771.
8. Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137.
9. For syntheses of muricatacin from optically active starting materials, see: (a) Figadere, B.; Harmange, J.-C.; Laurens, A.; Cave, A. *Tetrahedron Lett.* **1991**, *32*, 7539; (b) Pelletier, C. G.; Saniere, M.; Charvet, I.; Merrer, Y. L.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 115; (c) Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 817; (d) Saniere, M.; Charvet, I.; Merrer, Y. L.; Depezay, J.-C. *Tetrahedron* **1995**, *51*, 1653; (e) Yoon, S.-H.; Moon, H.-S.; Hwang, S.-K.; Choi, S. R.; Kang, S.-K. *Bioorg. Med. Chem.* **1998**, *6*, 1043.
10. For a synthesis of muricatacin by kinetic resolution, see: Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1993**, *34*, 1597.
11. For syntheses of muricatacin using enantioselective methods, see: (a) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha, A.-B.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407; (b) Marshall, J. A.; Welmaker, G. S. *J. Org. Chem.* **1994**, *59*, 4122; (c) van Aar, M. P. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 11223; (d) Solladie, G.; Hanquet, G.; Izzo, I.; Crumbie, R. *Tetrahedron Lett.* **1999**, *40*, 3071.
12. Chandrasekhar, M.; Raina, S.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 4969.
13. Raina, S.; Singh, V. K. *Tetrahedron* **1996**, *52*, 4479.
14. (a) Kierstead, R. W.; Faraone, A.; Mennona, F.; Mullin, J.; Guthrie, R. W.; Crowley, H.; Simko, B. *J. Med. Chem.* **1983**, *26*, 1561; (b) Jurczak, J.; Bauer, T.; Chimielewski, M. *Carbohydr. Res.* **1987**, *164*, 493.
15. Saravanan, P.; Chandrasekhar, M.; Anand, R. V.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 3091.
16. The specific rotation of (–)-**1d**: $[\alpha]_D^{25}$ –23.5 (*c* 0.43, $CHCl_3$) {lit.[8] $[\alpha]_D^{25}$ –23.3 (*c* 1.8, $CHCl_3$).