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ENANTIOSELECTIVE SYNTHESIS OF (-)-SARRACENIN USING D-GLUCOSE AS CHIRAL TEMPLATE

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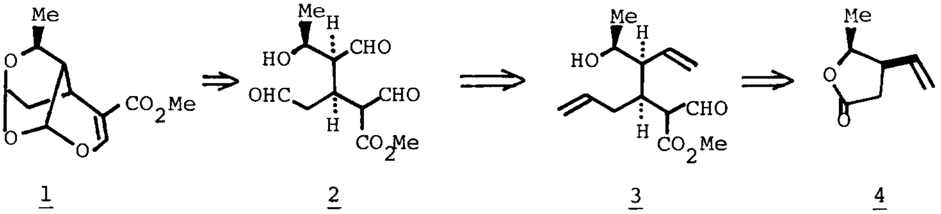
Summary: Enantioselective synthesis of the iridoid monoterpene (-)-sarracenin (1) has been accomplished using D-glucose as chiral template.

Sarracenin (1) is a tricyclic monoterpene which was isolated from the insectivorous golden trumpet (Sarracenin flavia)[1]. Recently, the synthesis [2,3,4] of sarracenin (1) has attracted great interest not only because of its unique structural feature but also its potential utility for the synthesis of the biosynthetically related compound, such as secologanin and ajmalicine[5]. We now describe a novel enantioselective synthesis of (-)-sarracenin (1) from D-glucose.

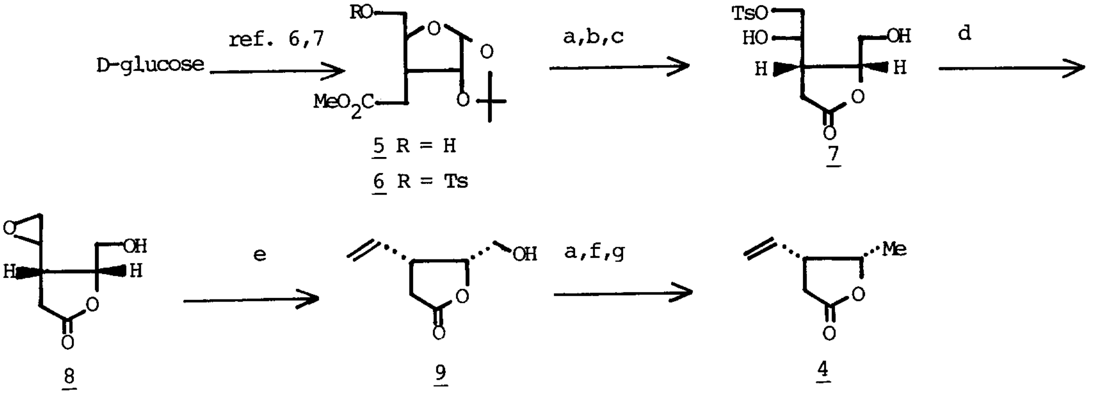
Scheme I



Our strategy leading to (1) was based on the transformation of the chiral lactone (4) into the functional equivalent of the trialdehyde (2) through stereo- and regioselective introduction of requisite carbon units, followed by oxidative cleavage of olefinic double bonds.

The synthesis of the chiral lactone (4) was accomplished as outlined in Scheme II. The chiral acetonide (5)[6], $[\alpha]_D+69.7^o$ ($CHCl_3$), prepared stereoselectively from D-glucose according to the known method [7,8], was converted to the tosylate (6) which was successively subjected to acid hydrolysis (0.5 % H_2SO_4 / aq. dioxane, reflux) and reduction with sodium borohydride (MeOH, 0°C) to give the diol (7) in good yield (> 90 %). Treatment of (7) with potassium carbonate (acetone, rt) gave the epoxide (8) almost quantitatively. Reduction of (8) using sodium iodide and zinc under buffered conditions[9] (AcONa / AcOH, 0° C) allowed the formation of the vinyllactone (9)[10,11], $[\alpha]_D$-57.8° ($CHCl_3$), in 52 % overall yield from (5). Conversion of the hydroxymethyl group of (9) to the methyl group by the standard method afforded the methylvinyllactone (4), bp_{25} 110°C (kugel rohr), $[\alpha]_D$-53.0° ($CHCl_3$), δ1.20 (3H,d, $-OCHCH_3$), 4.68 (1H, quint, -OCH-), 4.69 -6.10 (3H, m, CH_2=CH-), in 70 % yield.

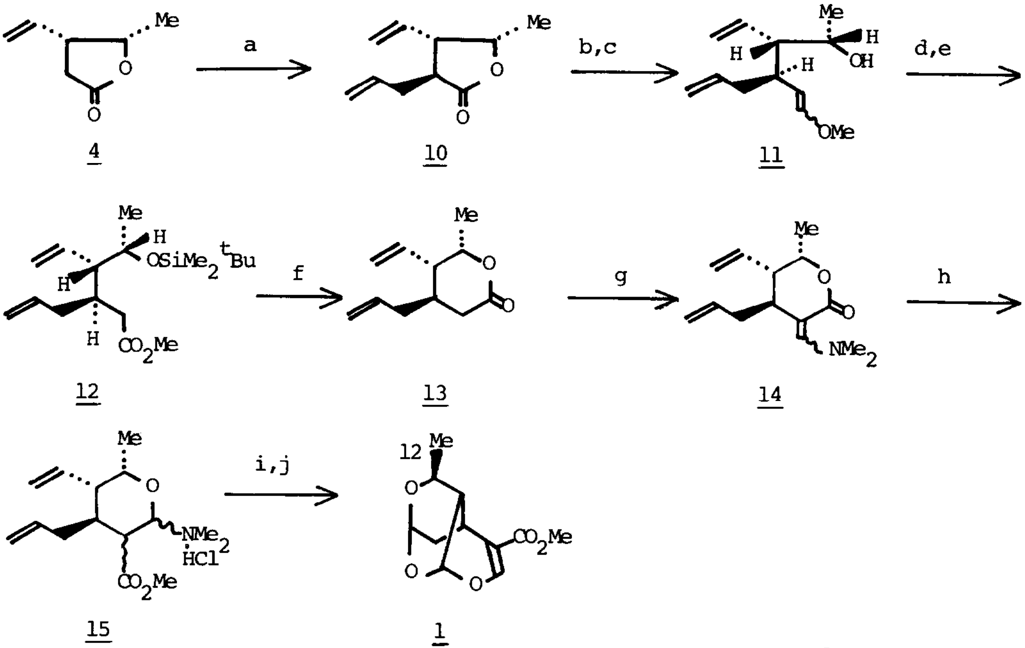
Scheme II



a) p-TsCl, pyridine, rt; b) 0.5% H_2SO_4/aq.dioxane, reflux; c) $NaBH_4$, MeOH, 0°C;
d) K_2CO_3, acetone, rt; e) NaI/Zn, AcONa/AcOH, 0°C; f) NaI, acetone, reflux;
g) $^nBu_3SnH$, AIBN, EtOH, rt.

Having the key chiral lactone (4) in hand, construction of the functional equivalent of (2) was then investigated. Treatment of (4) with allyl bromide in the presence of lithium diisopropylamide (THF, -78°C) allowed highly stereoselective alkylation[12] to give the allyllactone (10), $[\alpha]_D$-27.8° ($CHCl_3$), in 79 % yield. After reduction of (10) with diisobutylaluminum hydride (CH_2Cl_2, -78°C), the resulting lactol was subjected to Wittig reaction using α-methoxymethyl triphenyl phosphorane (glyme, rt) furnishing the enol ether (11) in 93 % yield as an 1 : 4 isomeric mixture. Since successive treatment with dil. sulfuric acid and Jones reagent afforded the δ-lactone (13) in only 20 % yield, the following alternative route was developed. Thus, protection of (11) as its tert-butyldimethylsilyl ether ($^tBuMe_2SiCl$ / imidazole, DMF, rt), followed by oxidation[13] with pyridinium chlorochromate (CH_2Cl_2, rt) gave the ester (12), $[\alpha]_D$-14.0^o ($CHCl_3$), which upon acidic methanolysis (p-TsOH, MeOH, reflux), yielded the lactone (13), $[\alpha]_D$-86.5^o ($CHCl_3$), in 74 % overall yield from (11).

Scheme III



a) LDA, CH_2=CHCH$_2$Br, THF, -78°C; b) DIBAH, CH_2Cl_2, -78°C; c) $Ph_3\overset{+}{P}\overset{Cl}{C}H_2OMe$, KO^{t}Bu, glyme, rt; d) $^tBuMe_2SiCl$/imidazole, DMF, rt; e) PCC, CH_2Cl_2, rt; f) p-TsOH, MeOH, reflux; g) $Me_2NCH(OMe)_2$, 170°C; h) 5% HCl-MeOH, rt; i) O_3, MeOH, -78°C then Me_2S; j) 90% aq.AcOH, 80°C.

Heating the lactone (13) with N,N-dimethylformamide dimethly acetal[14,15] in a sealed tube (170^o, 3 days) gave the vinylogous urethane (14) which was then subjected to acidic methanolysis with concomitant lactone-acetal rearrangement[16] to afford an isomeric mixture of the cyclic aminoacetal hydrochloride (15)[17]. Without purification, Ozonolysis of (15) (MeOH, -78^{o}C), followed by dimethyl sulfide work-up yielded the functional equivalent of (2) which upon dehydrative cyclization (90 % aq. AcOH, 80^o), furnished (-)-sarracenin (1), mp 127-127.5^{o}C (lit.[1] 127-128^{o}C), $[\alpha]_D$-24.3^o ($CHCl_3$) (lit.[3] -20.9^o ($CHCl_3$))[18], in 50 % overall yield from (13). The spectral data (^{1}H-NMR, IR, MS) of the synthetic substance were identical with those reported[1].

The study outlined above demonstrates an effective chiral route to the secoiridoids and the methodology developed is also applicable to the synthesis of secoiridoids which are functionalized at C-12.

References and Notes

1. D. H. Miles, U. Kokpol, J. Bhattacharya, T. L. Atwood, K. E. Stone, T. A. Bryson, and C. Wilson, J. Am. Chem. Soc., 98, 1569 (1976).
2. J. K. Whitesell, R. S. Matthews, and A. M. Helbling, J. Org. Chem., 43, 784 (1978); idem, J. Am. Chem. Soc., 103, 3468 (1981).
3. S. W. Baldwin and M. T. Crimmins, J. Am. Chem. Soc., 104, 1132 (1982).
4. L. F. Tietze, K.-H. Glusenkamp, M. Nakane, and C. R. Hutchinson, Angew. Chem. Int. Ed. Engl., 21, 70 (1982).
5. Miles suggested[1] that a suitably hydrated sarracenin might be a possible precursor of the nontryptohan portion of indole alkaloids such as ajmalicine.
6. All new compounds reported in this work gave satisfactory spectral (NMR, IR, MS) and analytical (high resolution MS) data.
7. O. T. Schmidt, Methods Carbohydr. Chem., 2, 320 (1963).
8. A. Rosenthal and L. Nguyen, J. Org. Chem., 34, 1029 (1969).
9. J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, J. Chem. Soc., 112 (1959).
10. Recently, the synthesis of the enantiomer of (9) has been reported[11]. Specific rotation was compared as its tert-butyldimethylsilyl ether (reported $[\alpha]_D +13.9^o$ ($CHCl_3$); ours $[\alpha]_D -43.5^o$ (($CHCl_3$)).
11. T. Kametani, T. Suzuki, M. Nishimura, E. Sato, and K. Unno, Heterocycles, 19, 205 (1982).
12. S. Takano, W. Uchida, S. Hatakeyama, and K. Ogasawara, Chemistry lett., 733 (1982).
13. G. Piancatelli, A. Scettri, and M. D'Auria, Tetrahedron Lett., 3483 (1977).
14. G. Buchi and J. A. Carlson, J. Am. Chem. Soc., 90, 5336 (1968); R. F. Abdulla and K. H. Fuhr, J. Org. Chem., 43, 4248 (1978).
15. Introduction of a formyl unit by hydroxymethylenation (LDA, HCO_2Me, THF, rt) was unsuccessful.
16. F. Korte and H. Machleidt, Chem. Ber., 88, 136 (1955).
17. The corresponding pure aminoacetal could not be obtained from preparative TLC (SiO_2, 1 : 1 Et_2O-hexane) presumably because of the partial formation of the hemiacetal during isolation. However, aqueous extraction of the crude hydrochloride (15) followed by reextraction with methylene chloride after basification gave the practically pure aminoacetal.
18. Baldwin and Crimmins pointed out[3] that ambiguity concerning the specific rotation of the natural material made a valid comparison difficult.

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