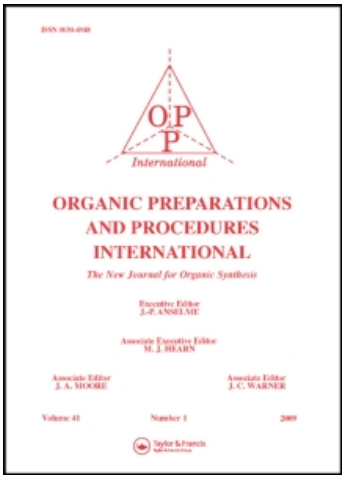

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SYNTHESIS OF (S)-(+)PANTOLACTONE

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SYNTHESIS OF (S)-(+)PANTOLACTONE

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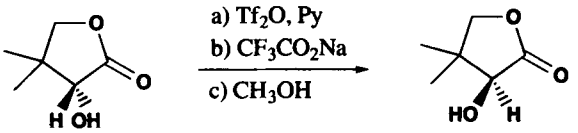
(R)(-)Pantolactone, a degradation product of natural pantothenic acid, is a commercially available compound widely used as chiral auxiliary in asymmetric synthesis. The (S)(+) isomer which is often needed, is unfortunately not commercially available. It can be obtained either by resolution of the racemic mixture or by asymmetric synthesis. Apart from stereoselective hydrogenation of ketopantolactone (ee <80%),[1] the simplest asymmetric synthesis of the S-enantiomer would be an inversion of configuration starting from (R)(-) pantolactone. However, pantolactone is a hindered secondary alcohol which is not prone to inversion of configuration. For instance, the method fails when pantolactone is subjected to a Mitsunobu reaction.[2] A solution to this problem proposed by Corey[3] consisted in the use of a triflate ester. The S_2N substitution was then easily achieved with potassium acetate at 60° for 2 hrs and the corresponding pantolactone acetate was saponified with lithium hydroxide, giving (S)(+) pantolactone in 90% yield and 97% ee. This procedure was recently improved by Moriarty *et al.*[4] who suggested the use of potassium nitrite with a catalytic amount of 18-crown-6 in place of potassium acetate, thus allowing the reaction to take place at room temperature. These authors claimed an 89% overall yield and 100% inversion (from $[\alpha]_D$ measurements).



We propose here an alternative to this later improvement which consists of replacing potassium nitrite by sodium trifluoroacetate. Under these conditions, the S_2N substitution takes place rapidly at room temperature and the resulting trifluoroacetate moiety can be readily transesterified under mild conditions with methanol. (S)(+) Pantolactone was thus obtained in 95% yield with an enantiomeric excess greater than 99% as measured by NMR (more accurate than polarimetry). This procedure avoids both a possible racemizing saponification occurring in Corey's method[3] and a long reaction time (24-36 hrs) necessary in Moriarty's procedure[4] to complete the S_2N substitution.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi apparatus and are uncorrected. Optical rotations were obtained with a Perkin-Elmer Model 241 polarimeter. ^1H NMR spectra were recorded on a Brucker AC-250 spectrometer with TMS as internal standard.

(S)-(+)Pantolactone.- To a stirred solution of triflic anhydride (3 mL, 18.3 mmoles, 1.5 equiv) and pyridine (3 mL) in dichloromethane (20 mL) at -20° was added a solution of commercially available (R)(-) pantolactone (1.69g, 13 mmoles) in dichloromethane (5 mL). After stirring for 1 hr at the same temperature, the solution was poured onto a water-ice mixture (100g) saturated with sodium bicarbonate and stirring was continued for a further hr. The separated organic layer was washed successively with a cold 1N HCl solution and brine and was then dried over $MgSO_4$. The solvent was removed under vacuum and the unpurified residual oily triflate ester was used in the next step.

Sodium trifluoroacetate (10.6g, 6 equiv) was slowly added to a solution in DMF (20 mL) of the triflate ester prepared as described above. The resulting slurry was stirred for 3 hrs at room temperature and was then filtered and the DMF removed under reduced pressure. The resulting oil was dissolved in methanol (25 mL) and the solution was stirred for 2 hrs at room temperature. The methanol was removed and pure (S)(+)pantolactone, mp. 89°, was obtained (1.55 g., 92%)[5] by passing through a column of silica gel with 1:1 ether-hexane as eluent, $[\alpha]_D^{22°}$ = +49.6° (c = 1, $CHCl_3$), lit[4] $[\alpha]_D^{23°}$ = +49.9° (c = 1, $CHCl_3$). The optical purity of pantolactone (ee >99%) was determined accurately using Parker's procedure,[6] by examination of the NMR spectrum of the compound resulting from condensation at -10° of (S) O-acetylmandelic acid with 0.9 equiv of pantolactone (no S,R diastereoisomer detected).

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