

NOVEL (4 + 1) FRAGMENT COMBINATION APPROACH TO CHIRAL
CYCLOPENTANOIDS FROM TARTARIC ACID

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Abstract : A chiral cyclopentanoid building block 29 has been synthesized in a "one pot" cyclization process from epoxides 22 - 25 (which are readily accessible from (R,R)-(+)-tartaric acid) with the carbanion derived from phenylthioacetonitrile (PhS-CH₂-CN).

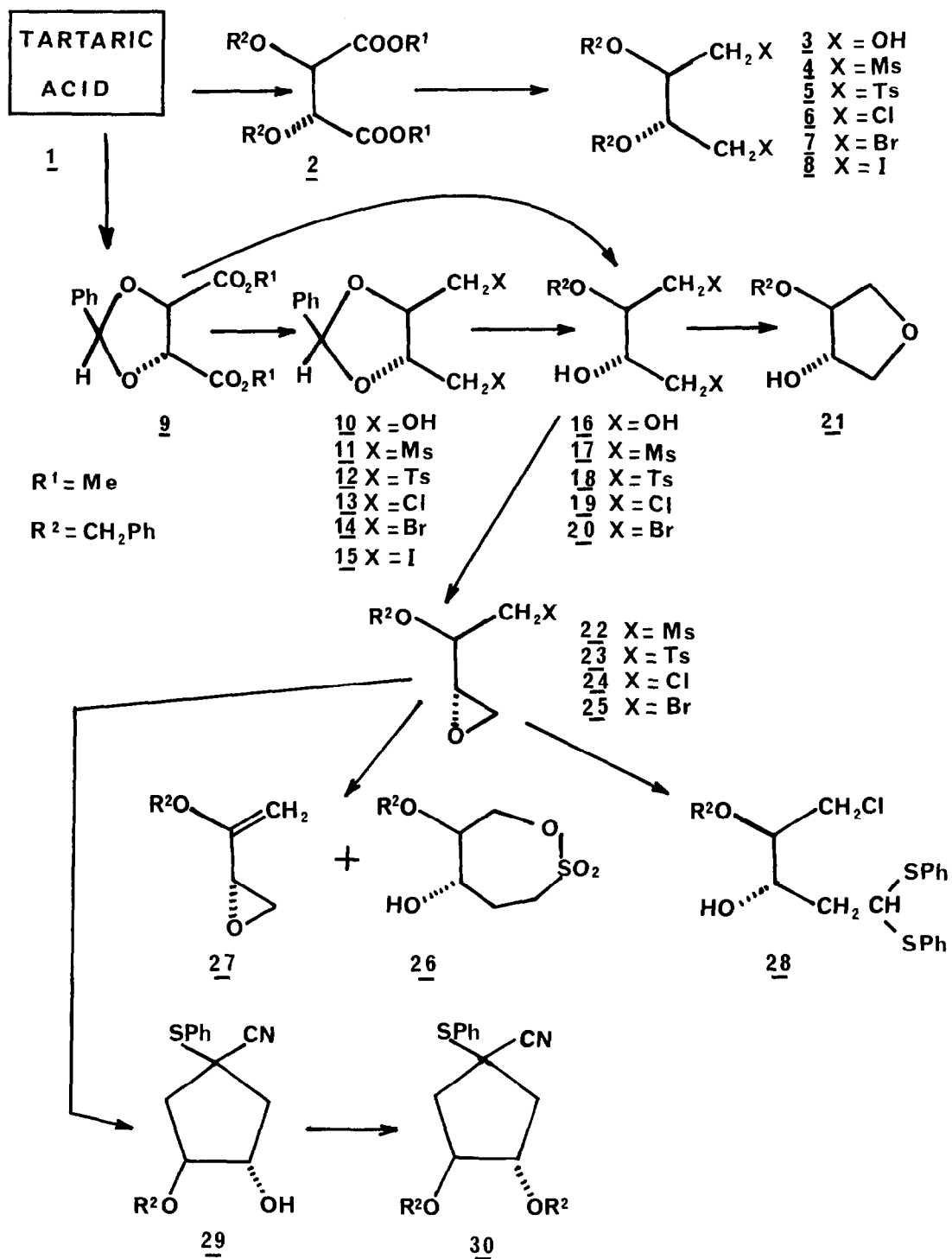
In view of the vast array of important cyclopentanoid natural products, their synthesis in optically pure form is a desirable objective. Few synthetic methods²⁻⁶ achieve this without resorting to classical resolution by chemical or microbiological means. In this and subsequent communications¹, we now report the preparation of such molecules from (R,R)-(+)-tartaric acid 1.

Tartaric acid 1 is a priori an attractive⁷ starting material since a) both enantiomeric forms are readily available, b) it possesses a C₂-symmetry.

Our approach - as originally conceived - was similar to that reported by Japanese workers, which involved an intramolecular cyclization⁸. However, all attempts to bring about such a cyclization by reaction of the 2,3-O-acetals 11 - 15 or the 2,3-di-O-ethers of L-threitol 4 - 8 with the carbanions derived from MeSCH₂SOMe, PhS-CH₂-SPh, PhS-CH₂-CN, PhS-CH₂-CO₂Et failed. We therefore explored an alternative route involving the reaction of the epoxides 22 - 25 derived from tartaric acid with different carbanions (Table, entries 1-11).

The required epoxides were initially prepared from the known 2-O-benzyl-L-threitol^{7,9} 16. However, the formation of 21 (25%) by intramolecular cyclization rendered this method unattractive.

S C H E M E



Table

Entry	Substrate	Reagent	Solvents Temperature	Base	Products Yields (%)
1	<u>24</u>	PhS-CH ₂ -SPh	Ether + TMEDA 0°C	nBu-Li	<u>28</u> (72)
2	<u>24</u>	PhS-CH ₂ -CN	Ether + TMEDA 0°C	nBu-Li	<u>27</u> + <u>29</u> (30 + 30)
3	<u>25</u>	PhS-CH ₂ -CN	Ether + TMEDA 0°C	nBu-Li	<u>27</u> + <u>29</u> (20 + 50)
4	<u>23</u>	PhS-CH ₂ -CN	Ether + TMEDA 0°C	nBu-Li	<u>23</u> + <u>29</u> (30 + 30)
5	<u>23</u>	PhS-CH ₂ -CN	DMF 0°C	NaHMDS	<u>27</u> + <u>29</u> (30 + 10)
6	<u>23</u>	p-MePhSO ₂ CH ₂ NC (TOSMIC)	DME + DMSO 20°C	nBu-Li	<u>27</u> (50)
7	<u>22</u>	CH ₃ S-CH ₂ -SOCH ₃	DMF 0°C	NaHMDS	<u>26</u> (50)
8	<u>22</u>	PhSCH ₂ CO ₂ R	DMF	NaHMDS	<u>26</u> (50)
9	<u>22</u>	NC-CH ₂ SCSNMe ₂	DMF 0°C	NaHMDS	<u>26</u> (50)
10	<u>22</u>	PhSO ₂ -CH ₂ -CO ₂ Et	DMF 20°C	NaHMDS	<u>26</u> (50)
11	<u>22</u>	PhS-CH ₂ -CN	DMF 0°C	NaHMDS	<u>29</u> (70)

An alternative route for the preparation of the epoxides 22 - 25 involved the sodium borohydride diglyme reduction of the dimethyl-2,3-benzylidene tartrate 9 to the corresponding diol 10, followed by either mesylation or tosylation to afford 11 - 12. The corresponding bromide 14 was then easily obtained by conventional nucleophilic substitution of 11 and 12 using lithium bromide in diglyme. Subsequent reductive ring opening of 11, 12 and 14 with sodium cyanoborohydride^{10,11} in acetonitrile provided the monoalcohol derivatives 17, 18 and 20 (80-85%). The conversion of these compounds to epoxides 22, 23 and 25 was accomplished in excellent yield using sodium methoxide in methanol. The problem then remained to construct the relatively strained cyclopentane nucleus.

As can be seen (Table) the formation of the cyclopentane nucleus proved to be troublesome but possible. Elimination to 27, formation of sultone 26 and decomposition were observed with most carbanions and under a variety of conditions.

However, it was found that the anion derived from phenylthioacetonitrile reacted with epoxide 22 in the desired manner to give functionalized cyclopentane 29 (entry 11).

Thus, generation of the anion (sodium hexamethyldisilazide- NaHMD - in toluene) followed by addition of 22 in dimethylformamide gave 29 (70%). The corresponding *O*-benzyl derivative 30 was prepared by the usual benzylation procedure in excellent yield; [α]_D²⁵ +28° (c 0.85, CHCl₃).

It is noteworthy that reaction of the chloro-epoxide 24 with the lithio derivative of bis(phenylthio)methane yielded exclusively the acyclic product 28 in excellent yield (72%) (Table, entry 1). The conversion of 29 to other cyclopentanoids will be published in the subsequent communication.^{1,12}

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