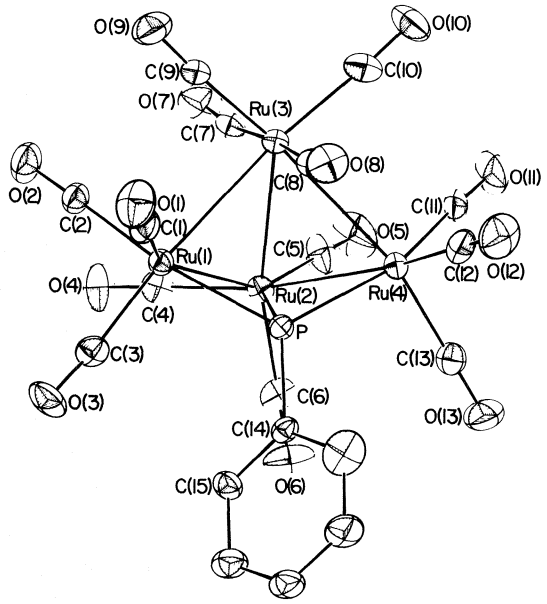

FIG. 2. The molecular structure of $Ru_4(CO)_{13}(\mu_3\text{-PPh})$ showing the atomic numbering. Important bond lengths and angles not included in the text are: Ru(1)—Ru(2) 2.833(1), Ru(1)—Ru(3) 2.861(1), Ru(2)—Ru(3) 2.974(1), Ru(2)—Ru(4) 2.784(1), Ru(3)—Ru(4) 2.924(1) Å; Ru(1)—P—Ru(2) 74.3, Ru(1)—P—Ru(4) 121.1(1), Ru(2)—P—Ru(4) 72.6°.

rapidly adds a second molecule of H_2 leading to an unstable dihydrido (μ_2-η^2-vinyl) complex $H_2Ru_3(CO)_8(PPh_2)(HC{=}C(H)Bu^t)$, **VII**. Under CO **VII** is quantitatively transformed into **III** with loss of *t*-butylethylene. Complex **III** reacts more slowly with CO to yield the coordinatively saturated species $Ru_3(CO)_{10}(H)(PPh_2)$. Carbon monoxide is not, however, required in the direct hydrogenative conversion of **II** to **III**. Complete spectroscopic and structural characterisation of these species will be described elsewhere. It is clear, however, that reduction of μ_3-η^2-acetylido clusters with H_2 under mild conditions is a useful strategy for the synthesis of hydrido-phosphido and hydrido-phosphinidene bridged clusters. Furthermore, our studies indicate that the reactivity of phenyl phosphido bridges under reducing conditions may limit the application of PPh_2 bridged clusters in catalysis.[3]

Acknowledgements

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[3]Complete set of supplementary material is available, at a nominal charge, from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Ont., Canada K1A 0S2.

Studies toward polyether antibiotics: stereospecific synthesis of polysubstituted tetrahydropyrans

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A stereospecific and general method for the preparation of *trans*-tetrahydropyrans **1** and *cis*-tetrahydropyrans **2** from acyclic precursors are described. Compound **12**, a possible intermediate for the synthesis of antibiotic X-14547A, has been synthesized.

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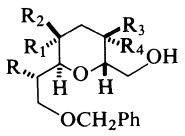
On décrit une méthode générale de synthèse stéréospécifique des tétrahydropyrannes *trans* (**1**) et des tétrahydropyrannes *cis* (**2**) à partir de précurseurs acyliques. On a synthétisé le composé **12** qui est un intermédiaire éventuel dans la synthèse de l'antibiotique X-14547A.

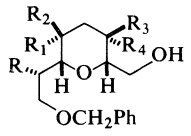
[Traduit par le journal]

The polyether antibiotics represent a growing and important class of naturally occurring substances. These compounds have received considerable attention in the synthetic field during recent years, because of their unique ionophoric properties as well as the degree of stereochemical complexity of this class of compounds (1). As a part of our program aimed at the synthesis of a variety of ionophore antibiotics, we have been interested in developing a stereospecific and general method for synthesizing the highly substituted tetrahydropyranyl ring systems **1** and **2** from acyclic intermedi-



1

a: R = R_4 = Me, R_1 = R_2 = R_3 = H
(ring A of antibiotic X-14547A)
b: R = Et, R_4 = Me, R_1 = R_2 = R_3 = H
(ring A of salinomycin)
c: R = R_2 = Me, R_1 = R_3 = R_4 = H
(ring A of nigericin)



2

a: R = R_2 = Me, R_1 = R_3 = R_4 = H
(ring A of antibiotic X-206)
b: R = R_2 = R_3 = Me, R_1 = R_4 = H
(ring A of alborixin)

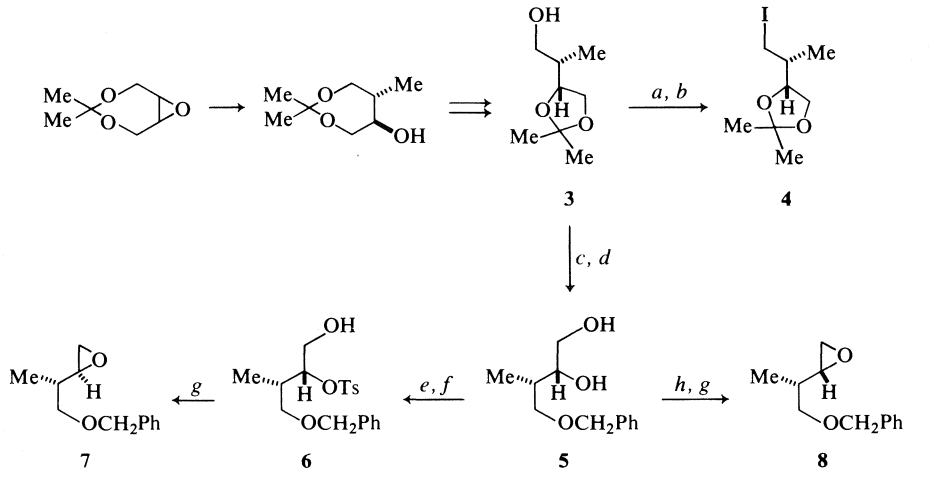
ates. The structural ring systems in the present studies have often been found in the polyether antibiotics. The *trans*-tetrahydropyrans **1** represent ring A of antibiotic X-14547A (for isolation, see ref. 2*a*, for syntheses of the "right wing", see ref. 2*b*–*d*), salinomycin (3), and nigericin (4), while the *cis*-tetrahydropyrans **2** represent ring A of antibiotic X-206 (5) and alborixin (6). Although for future total syntheses of polyether antibiotics, chiral precursors for the construction of tetrahydropyranyl subunits are a crucial point, our exploratory work for the present studies was undertaken with racemic materials.

The starting material **3** for the present investigation was prepared by a modification of literature procedures (7) from commercially available (*Z*)-2-butene 1,4-diol (Scheme 1). The key reaction in the preparation of the enantiomeric pair of the alcohol **3** was the stereospecific *trans* opening of the epoxide with lithium dimethylcuprate. Compound **4**[1] was obtained in quantitative yield by two-step standard procedures from the corresponding primary alcohol **3**. In order to explore the stereospecificity and feasibility of our approach to the tetrahydropyranyl ring systems, two isomeric epoxides **7** and **8** were synthesized from the same enantiomeric pair of alcohol **3** in a straight-forward and unambiguous manner (Scheme 1). The alcohol **3** was converted into the diol **5** in 95% yield by benzylation and mild acidic hydrolysis. For the preparation of the α-epoxide **7**, treatment of the diol **5** with *p*-anisyldiphenylmethyl chloride (1.1 equiv) in pyridine at 0°C overnight and then subsequently with tosyl chloride (1.2 equiv) at room temperature for 1 day gave the crude product, which was treated with 80% aqueous acetic acid at room temperature for 4 h to yield the hydroxyl tosylate **6**. The yield was 84% from the diol **5**. This operation was to invert the configuration at the secondary alcohol when the epoxide was formed in the next step. Exposure of compound **6** to methanolic potassium hydroxide at room temperature for 1 h led to the formation of the desired epoxide **7** in 89% yield. For the preparation of the β-epoxide **8**, the diol **5**, on treatment with tosyl chloride (1 equiv) in pyridine and methylene dichloride at 0°C for 6 h, followed with methanolic potassium hydroxide at room temperature for 1 h furnished the epoxide **8** in 86% yield.

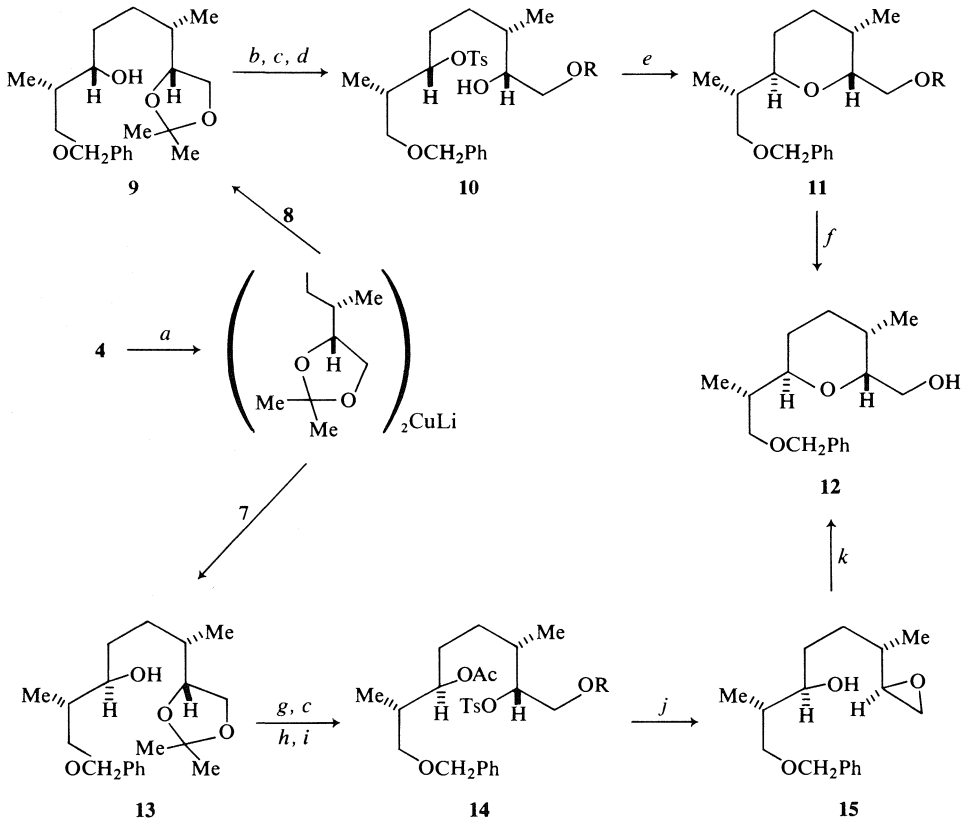
Two alternative elaborations of *trans*-tetrahydropyran **1** by the sequence of reactions shown in Scheme 2 were examined. Thus, treatment of the iodide **4** with *n*-butyllithium (1.1 equiv) in tetrahydrofuran at −70°C for 4 h, followed with cuprous iodide at the same temperature for 1 h resulted in the formation of lithium cuprate derivative, which reacted in the desired manner with the epoxide **8** (the ratio of epoxide-to-iodide was 1 equiv:1.7 equiv) at −70°C for 2 h to give the alcohol **9** in 65–70% yield.[2] Conversion of **9** to the hydroxyl

[1]Satisfactory physical and spectral data have been obtained for all new compounds.

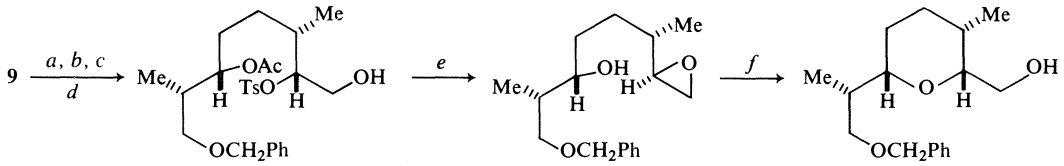
[2]The material obtained from this reaction, as expected, was a pair of diastereoisomers as shown by ^{13}C nmr, which could not be separated by HPLC.



SCHEME 1. Reagents and conditions: *a*, TsCl, pyridine, RT; *b*, NaI, acetone, RT, 2 days; *c*, NaH, $PhCH_2Br$, THF, RT; *d*, 80% aqueous HOAc, RT, 6 h; *e*, *p*-anisyldiphenylmethylchloride (1.1 equiv), pyridine, 0°C, 12 h, then TsCl (1.2 equiv), RT, 1 day; *f*, 80% aqueous HOAc, RT, 4 h; *g*, KOH, MeOH, RT, 1 h; *h*, TsCl (1 equiv), pyridine, CH_2Cl_2, 0°C, 10 h.



SCHEME 2. R = *p*-anisyldiphenylmethyl. Reagents and conditions: *a*, *n*BuLi (1.1 equiv), THF, −70°C, 4h, then CuI, −70°C, 1 h; *b*, TsCl, pyridine, RT; *c*, 80% aqueous HOAc, RT; *d*, *p*-anisyldiphenylmethyl chloride (1.1 equiv), pyridine, RT; *e*, NaH (1.4 equiv), benzene, reflux, 6 h; *f*, 80% aqueous HOAc, RT; *g*, Ac_2O, pyridine, RT; *h*, *p*-anisyldiphenylmethyl chloride (1.1 equiv), pyridine, RT, 6 h, then TsCl (1.2 equiv), RT, 1½ day; *i*, 80% aqueous HOAc, RT, 4 h; *j*, KOH, MeOH, RT, 10 h; *k*, HOAc, RT, 2 days.



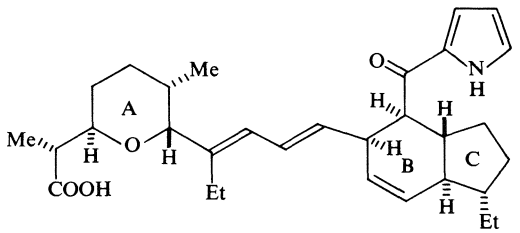
16 17 18

SCHEME 3. Reagents and conditions: *a*, Ac_2O, pyridine, RT; *b*, 80% aqueous HOAc, RT; *c*, *p*-anisyldiphenylmethyl chloride (1.1 equiv), pyridine, RT, 6 h, then TsCl (1.2 equiv), RT, 1½ day; *d*, 80% aqueous HOAc, RT, 4 h; *e*, KOH, MeOH, RT, 10 h; *f*, HOAc, RT, 2 days.

tosylate **10** was accomplished in 81% yield by standard procedures, tosylation of the secondary alcohol, generation of the diol by mild acidic hydrolysis, and tritylation of the primary alcohol (Scheme 2). With the complete carbon skeleton and functionality assembled, the *trans*-tetrahydropyranyl ring **11** was smoothly formed in 69% yield by the reaction of compound **10** with sodium hydride (1.4 equiv) in anhydrous benzene under reflux for 6 h.[3] The cyclization reaction from the acyclic intermediate achieved by a S_N2 displacement reaction left no doubt about the outcome of the desired stereochemistry of the *trans*-tetrahydropyranyl ring system. Compound **11**, on treatment with 80% aqueous acetic acid at room temperature, afforded quantitatively compound **12**. An alternative route to *trans*-tetrahydropyran **12** was also developed starting with alcohol **13**[2] prepared by the reaction of α-epoxide **7** with the iodide **4** under the same conditions as described above, and proceeding (Scheme 2) via the intermediates **14** and **15**. The overall yield from **7** and **4** to **15** was 53%. When compound **15** was treated with glacial acetic acid at room temperature for 2 days, the cyclization reaction proceeded smoothly to give the identical compound **12** in 92% yield. That two independent routes yielded the identical *trans*-tetrahydropyranyl ring affirm to the complete stereospecificity of the epoxide opening reaction with acetic acid. Clearly, the simplicity and high yield of this approach to compound **12** compared with the first approach make the reaction more attractive to the synthesis of polysubstituted tetrahydropyranyl ring systems.

With the successful development of the *trans*-tetrahydropyran synthesis, we now shifted our direction to the *cis*-ring systems **2**. Scheme 3 summarizes the sequence of reactions for the *cis*-series. Using the same techniques for the preparation of compound **15** from compound **13**, the alcohol **9** was converted into compound **17** in 69% overall yield. Treatment of the hydroxyl epoxide **17** with glacial acetic acid at room temperature for 2 days led to the isolation of the *cis*-tetrahydropyran **18** in 90% yield.[4]

The efficiency and stereospecificity of our method for the construction of various tetrahydropyranyl systems will open a wide synthetic application for many polyether antibiotics. Specifically, compound **12**, which possesses the correct stereochemistry and the required functionality for the synthesis of the recently isolated novel antibiotic X-14547A **19** (2), will be used as a key intermediate for the total synthesis. We are currently synthesizing the optically active compound **12** from tartaric acid and further progress along the line will be reported in due course.



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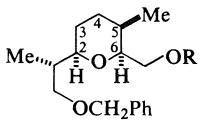
The author thanks the Natural Sciences and Engineering Research Council of Canada and

[3]After cyclization, the pair of diastereoisomers **11** and **i**, produced from the reaction of **4** with **8**, could easily be separated by column chromatography on silica gel in 1% methanol in hexane and CH_2Cl_2 (**i**, R_f 0.75; **11**, R_f 0.55). The



i

stereochemistry of **11** and **i** was assigned based on the chemical shift of their ^1H and ^{13}C nmr. Compound **11** gave ^1H nmr signal at 3.95 ppm and ^{13}C nmr signal at 72.9 ppm for hydrogen at C-6, while compound **i** had ^1H nmr signal at 3.72 ppm and ^{13}C nmr signal at 79.3 ppm for axial hydrogen at C-6.

[4]The pair of diastereoisomers was easily separated by column chromatography on silica gel. Compound **18** gave ^{13}C nmr signal at 81.3 ppm for C-6; while its isomer showed signal at 74.6 ppm for C-6 in its ^{13}C nmr spectrum.

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Thiol esters in organic synthesis. X.[1] A new approach to 1,5-ketols and 5-hydroxy esters using *S,S'*-diethyl dithiomalonate as an ethanol carbanion equivalent

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Michael addition of *S,S'*-diethyl dithiomalonate to conjugated enones and α,β-unsaturated esters followed by reduction with Raney nickel gave rise to 1,5-ketols and 5-hydroxy esters respectively in good yields.

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L'addition suivant Michael du dithiomalonate de *S,S'*-diéthyle à des énones conjuguées et à des esters α,β-non saturés, suivie par une réduction à l'aide de nickel de Raney conduit, suivant le cas, à la formation de cétols-1,5 et d'hydroxy-5 esters avec de bons rendements.

[Traduit par le journal]

In a recent communication (1*e*), we reported that *S,S'*-diethyl dithiomalonate reacts readily with alkyl halides and other electrophiles and that the dithiomalonate group can be easily reduced by Raney nickel under mild conditions to the ethanol level. One interesting application of *S,S'*-diethyl dithiomalonate as a convenient source of ethanol carbanion equivalent is its use as a Michael donor to facilitate the preparation of 1,5-ketols and 5-hydroxy esters, versatile synthetic intermediates which are particularly useful for the construction of six-membered carbocyclic and heterocyclic systems (2, 3).

In our initial attempts to induce the Michael addition of *S,S'*-diethyl dithiomalonate to α,β-unsaturated carbonyl compounds,[2] the use of the sodium and lithium salts generated *in situ* with strong bases such as NaH, NaSEt, and *t*-BuOLi was found to be ineffective. In each case, the starting material was recovered, presumably due to an unfavorable addition–elimination equilibrium. However, when a tertiary amine was used as a base, the conjugated addition occurred readily. Of several amines examined, 1,4-diazabicyclo[2.2.2]-octane (DABCO) was shown to be most effective, giving consistently high yields of the products under mild conditions. In a typical experiment, a solution of *S,S'*-diethyl dithiomalonate (720 mg, 3.74 mmol), DABCO (420 mg, 3.74 mmol), and 2-cyclohexenone (300 mg, 3.12 mmol) in 1,2-dimethoxyethane (10 mL) was stirred at room temperature under an argon atmosphere for 48 h. The reaction mixture was acidified with 1 *N* aqueous hydrochloric acid and extracted with chloroform. Drying ($MgSO_4$), filtration, and concentration gave the crude product which was purified by column chromatography on silica gel. Elution with a solution

[1]For parts I–IX of this series, see refs. 1*a*–*i* respectively.

[2]The addition of *S,S'*-diethyl dithiomalonate to ethyl acrylate was previously explored by Scheithauer and Mayer (4) using sodium methoxide in methanol to give a mixture of the mono- and bis-adduct in ca. 1:1 ratio.

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