

Stereoselective Synthesis of Polypropionate Units and Heterocyclic Compounds by Cyclopropylcarbinol Ring-Opening with Mercury(II) Salts

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ABSTRACT

The mercury(II)-mediated electrophilic ring-opening reaction of various cyclopropylcarbinol derivatives bearing adjacent stereocenters and a remote nucleophilic functional group provides a useful strategy for synthesizing compounds bearing several contiguous stereocenters. These highly diastereoselective reactions occur with anchimeric assistance by the internal nucleophilic moiety and afford synthetically valuable building blocks such as polypropionate units or heterocyclic compounds. The application of cyclopropylcarbinol ring-opening for the preparation of functionalized oxygen heterocycles in natural product synthesis is also outlined.

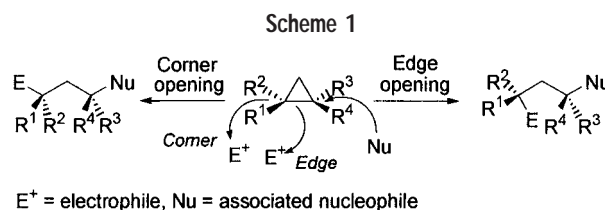
Introduction

Although the nucleophilicity of the carbon–carbon bond of cyclopropanes has been well described theoretically and experimentally for more than 100 years,¹ the most synthetically useful three-membered ring scissions promoted

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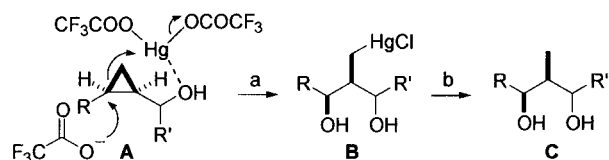
by electrophilic species have usually involved cyclopropylcarbinyl cations or related species,¹ cyclopropanes activated by electron-donating groups,^{2,3} and electrocyclic cleavage of dihalocyclopropanes.⁴ Even if cyclopropanes are much less nucleophilic than alkenes, they can react with electrophiles such as a proton,^{5,6} halogens,⁷ and transition^{2c,2e,8} or nontransition metal salts such as lead(IV),⁹ thallium(III),^{9c,10} and mercury(II).^{2b,3f,10c,11–18} The mechanism of the electrophilic ring-opening has been investigated and was demonstrated to involve a stereospecific “edge attack” for reagents capable of back-donation [halogens, Pd(II), Pt(II), ...], whereas the alternative “corner opening” mechanism was observed for poor back-donors [H⁺, Hg(II) and Tl(III) salts]. In both cases, the observed stereo- and regioselectivities are consistent with a scenario involving backside attack of the nucleophile at the carbon best able to stabilize a positive charge (Scheme 1).^{5–18}

Whereas a lot of investigations have focused on the understanding of the cyclopropane electrophilic ring-opening mechanism, few of them have been devoted to the synthetic application of these reactions. The development of stereocontrolled cyclopropanations promoted or catalyzed by various metals¹⁹ has led to a renewed interest in cyclopropane ring-openings, as they would indeed represent a powerful strategy for the elaboration of several contiguous stereogenic centers. One of the major breakthrough in this field is a report dealing with the oxymercuration of cyclopropylcarbinols.¹² Thus, cyclopropylcarbinols of type **A** were reported to undergo highly regioselective (>250:1) electrophilic ring-opening reactions when treated with mercuric trifluoroacetate, presumably controlled by the negative inductive effect of the hydroxyalkyl substituent, with concomitant highly stereoselective anti nucleophilic attack of the trifluoroacetate counteranion (>70:1). After treatment with a saturated aqueous solution of NaCl and reductive demercuration of the resulting organomercuric chlorides of type **B** with LiAlH₄,²⁰ 2-methyl-1,3-diols of type **C** were obtained (Scheme 2). Mercuric trifluoroacetate was found to be the most convenient mercuric salt in these transformations due to its high solubility in nonpolar organic solvents. Indeed, polar solvents which may compete with the substrate in ligating the mercury cation resulted in longer reaction

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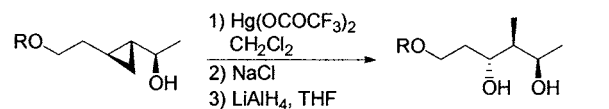
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Scheme 2



a) $\text{Hg}(\text{OCOCF}_3)_2$, CH_2Cl_2 then aq NaCl; b) LiAlH_4 , THF

Scheme 3



1a R = H

1b R = TBDPS

1c R = Ac

complex product mixtures

40%

2c R = Ac d.r. = 19:1

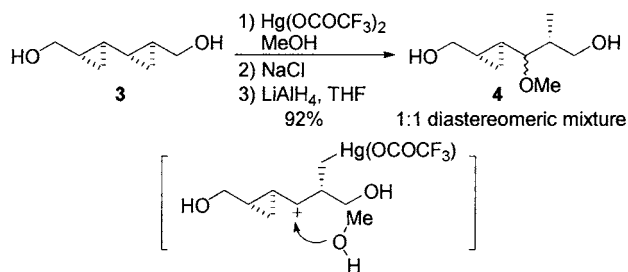
times.¹² Nevertheless, oxymercuration of cyclopropane derivatives can also be carried out in protic solvents (MeOH, BnOH, AcOH, ...) which directly act as nucleophiles and are therefore incorporated in the final product.^{11–16}

Besides reductive demercuration,²⁰ the carbon–mercury bond of organomercuric halides may be involved in a wide variety of subsequent transformations.²¹ Other related processes involve oxidation with molecular oxygen²² and radical-chain alkylations.²³ Organomercuric compounds can be transmetalated to organocopper reagents²⁴ and Kocovsky demonstrated the synthetic utility of several organomercurial cuprations coupled with subsequent intramolecular 1,2-additions to carbonyl compounds and 1,4-additions to Michael acceptors.^{10c,13} Organomercuric halides can be transmetalated to organopalladium¹⁴ or organorhodium²⁵ intermediates, and these transformations are of great synthetic value when used in conjunction with carbonylations. Therefore, the oxymercuration of cyclopropanes coupled with subsequent transformations of the intermediate organomercuric compounds nicely complement epoxide ring-opening with carbon nucleophiles, as both effect the addition of oxygen and carbon containing units across a carbon–carbon double bond.²⁶

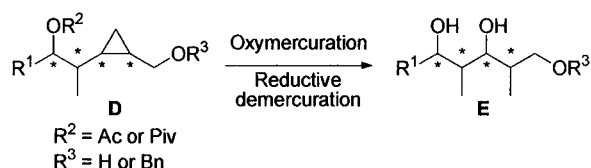
When the oxymercuration–reductive demercuration sequence was applied to a cyclopropylcarbinol bearing a homocyclopropylyc oxygen atom, complex product mixtures were obtained in the case of the free alcohol **1a** and the *tert*-butyldiphenylsilyl ether **1b**. On the contrary, for substrate **1c** having the remote alcohol moiety protected as an acetate, compound **2c** was obtained in moderate yield (40%) as a 19:1 diastereomeric mixture. Although an internal participation of the carbonyl group of the acetate was suggested, its critical role in the oxymercuration step remained unclarified. Furthermore, the structural assignment of the resulting final product **2c** was ambiguous since the remote acetate group had apparently surprisingly survived during the LiAlH_4 -promoted reductive demercuration step (Scheme 3).¹²

An interesting extension of the oxymercuration to bicyclopropane arrays was reported by Barrett.¹⁶ Although

Scheme 4



Scheme 5



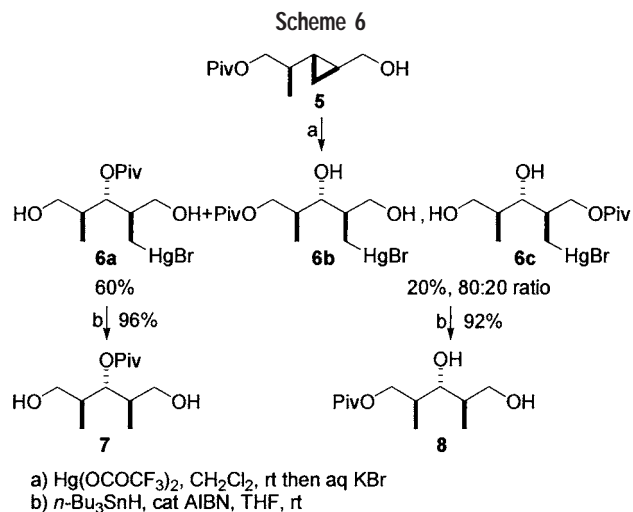
$\text{R}^2 = \text{Ac}$ or Piv
 $\text{R}^3 = \text{H}$ or Bn

the bicyclopropanedimethanol **3** reacted rapidly with mercuric trifluoroacetate in the presence of methanol, a mono ring-opening reaction leading to **4** occurred with essentially no diastereoselectivity. This result was explained by the ability of the second cyclopropane to stabilize the adjacent developing carbocation which is further trapped by methanol in a stereorandom fashion. Furthermore, the oxymercuration did not readily proceed further due to the fact that the cyclopropane in compound **4** became deactivated by the negative inductive effect of the two adjacent oxygenated moieties (Scheme 4).

Synthesis of Polypropionate Units from Cyclopropylcarbinol Derivatives

Since the cyclopropane could be regarded as an equivalent of a methyl–hydroxyl array whose relative configuration is controlled by the initial stereogenic centers of the three-membered ring, the oxymercuration–reductive demercuration of cyclopropylcarbinol derivatives of type **D** was investigated, with the aim of synthesizing polypropionate units of type **E**. The remote homocyclopropylyc oxygen atom of the cyclopropanes of type **D** was protected as an acetate or a pivalate ($\text{R}^2 = \text{Ac}$ or Piv) and the hydroxyl group of the cyclopropylcarbinol could be unprotected or protected as a benzyl ether ($\text{R}^3 = \text{H}$ or Bn) (Scheme 5).^{27,28}

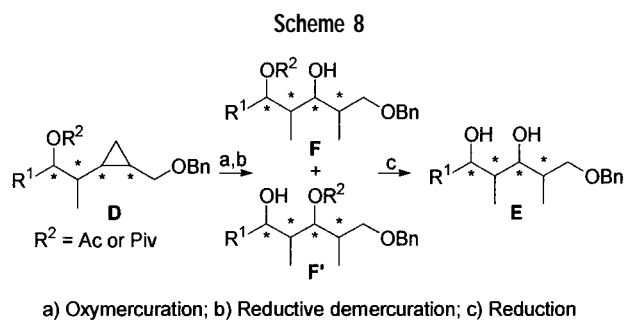
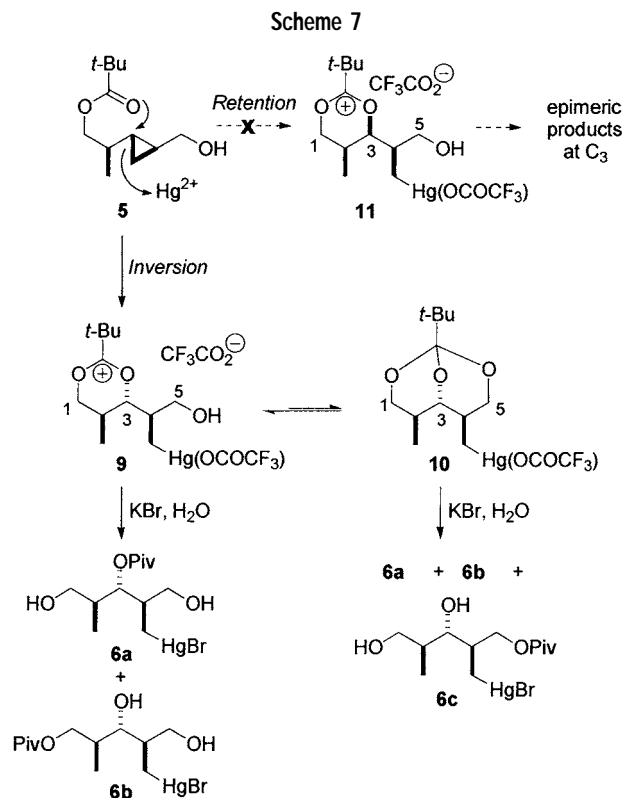
The crucial role of the ester protecting group for the remote homocyclopropylyc oxygen atom was demonstrated in the case of the racemic cyclopropanemethanol **5**. Indeed, this compound reacted rapidly with mercuric trifluoroacetate, and after treatment with KBr , the organomercuric bromides **6a** and an inseparable mixture of **6b** and **6c** (80/20 ratio) were isolated in 60% and 20% yields, respectively. Reductive demercuration with $n\text{-Bu}_3\text{SnH}$ and a catalytic amount of AIBN in THF ²⁰ converted the organomercuric **6a** to the stereotriad **7** (96%), whereas the **6b/6c** mixture was converted to the same stereotriad **8** (92%). It is worth noting that when the pivaloyl group in compound **5** was replaced by a *p*-methoxybenzyl ether, the oxymercuration failed despite extended reaction times (Scheme 6).²⁷



Thus, organomercuric bromides **6a–c** and stereotriads **7** and **8** all share the same stereochemical information, as they only differ by the positioning of the ester group. This result further highlights the dramatic influence of the remote ester moiety in the oxymercuration reaction. A reasonable mechanistic pathway involves an anchimerically assisted oxymercuration by the carbonyl group of the ester moiety, proceeding with inversion of configuration at C_3 and leading to a dioxacarbenium type intermediate **9**. Upon hydrolysis in the presence of KBr, this intermediate would generate the corresponding regioisomeric organomercuric bromides **6a** and **6b**. To explain the formation of the minor organomercuric bromide **6c**, the intermediacy of a bicyclic ortho ester **10** could also be envisaged,²⁹ and its subsequent hydrolysis would generate a mixture of the three organomercuric bromides **6a–c**. Apparently, products that would have resulted from an oxymercuration proceeding with retention of configuration (hydrolysis products derived from intermediate **11**) were not observed (Scheme 7).²⁷

Although the possibility of synthesizing stereotriads from cyclopropanemethanols of type **D** ($\text{R}^3 = \text{H}$) was demonstrated, regioisomeric mixture of products were obtained. To circumvent this drawback and synthesize polypropionate units from cyclopropanes of type **D** having the hydroxyl groups differentiated, the same sequence was investigated starting from the corresponding substrates protected as benzyl ethers ($\text{R}_3 = \text{Bn}$). Following the oxymercuration–reductive demercuration reaction, the regioisomeric mixtures of pivalates of type **F** and **F'** were subsequently converted to a single polypropionate unit of type **E** by reduction with LiAlH_4 (Scheme 8).

Several cyclopropanemethanols protected as benzyl ethers were therefore subjected to this three-step sequence, and the results are listed in Table 1. The corresponding polypropionate units were obtained as single diastereomers (25–65% overall yield), arising from an anchimerically assisted oxymercuration (by the carbonyl of the ester protecting group of the homocyclopropylic oxygen atom) proceeding with inversion of configuration at the stereocenter bearing the newly introduced oxygenated moiety.^{27,30}



Synthesis of Heterocycles by Mercury(II)-Mediated Cyclofunctionalization of Cyclopropylcarbinols

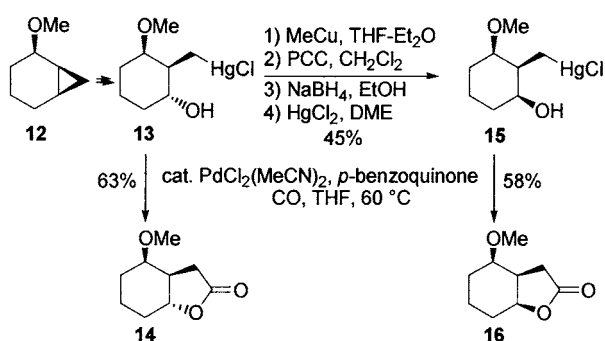
Two different approaches have been considered for the elaboration of heterocyclic compounds relying on the electrophilic ring-opening of cyclopropane derivatives with mercury(II) salts. According to a first approach, a standard intermolecular oxymercuration of the three-membered ring is initially carried out and the resulting organomercuric intermediate subsequently subjected to further synthetic manipulations, leading to the heterocyclic structure. This strategy is illustrated by the transformation of the organomercuric chloride **13**, resulting from the oxymercuration of **12**, to the *trans*-lactone **14** (63%) by carbonylation with carbon monoxide in the presence of a catalytic amount of a palladium(II) complex and *p*-benzoquinone as the reoxidant (Scheme 9).^{14a} Interestingly, methylation of **13** with methylcopper gave a dialkyl-organomercuric derivative which is stable to a number of reducing agent. Therefore, the relative configuration of the secondary alcohol could be inverted by an oxidation–stereoselective reduction and the organomercuric chloride

Table 1

Substrates	a,b,c	Products	Overall yield
			38%
			50%
			65%
			47%
			52%
			33%
			29%
			25%

^a Hg(OCOCF₃)₂, CH₂Cl₂, rt, then aq KBr. ^b *n*-Bu₃SnH, cat AIBN, THF, rt, or THF/toluene, 60 °C. ^c LiAlH₄, THF, 0 °C to room temperature.

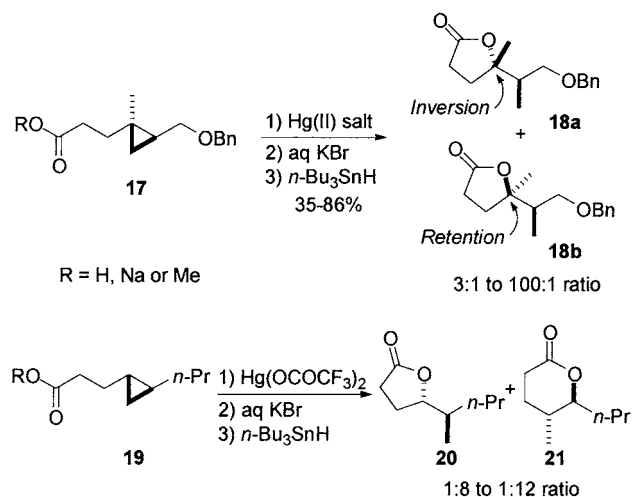
Scheme 9



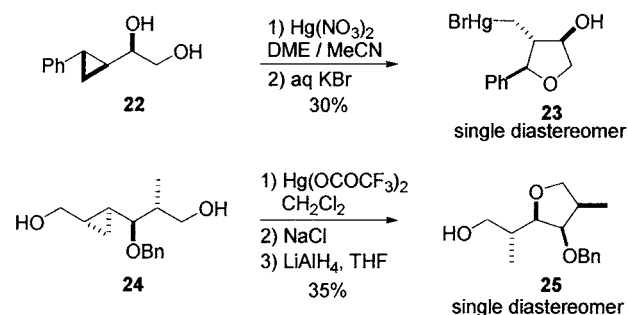
regenerated by addition of HgCl₂ to afford the corresponding epimeric compound **15**. Upon subsequent palladium-catalyzed carbonylation reaction, the *cis*-lactone **16** was obtained (58%) (Scheme 9).^{14b}

A second approach relies on the anchimeric assistance by a suitably located remote heteroatom containing functional group in the mercuriation of cyclopropanes and constitutes a powerful way of synthesizing heterocycles.^{16,17} Indeed, several mercury-mediated lactonizations of cyclopropane acid derivatives have been reported and the inherent regio- and stereoselectivities of these reactions have been studied. Thus, the cyclopropane **17** bearing a remote carboxylic acid functionality could be converted to a diastereomeric mixture of lactones **18a** and

Scheme 10



Scheme 11



18b by treatment with a mercury(II) salt and subsequent reductive demercuration. The corresponding sodium carboxylate or methyl ester derived from compound **17** also cyclized analogously and the observed stereoselectivities ranged from 3:1 up to 100:1 (inversion/retention ratio), depending on the substrates and the reaction conditions. However, for the electronically less-biased substrate **19**, regioisomeric mixtures of γ - and δ -lactones **20** and **21** (1:8 to 1:12 ratio) were respectively obtained with complete diastereoselectivity (inversion of configuration in each case) (Scheme 10).^{17a}

Similarly, substituted tetrahydrofurans **23** and **25** have been synthesized by mercury(II)-mediated cyclizations with hydroxy groups acting as internal nucleophiles in the case of cyclopropanes **22** and **24** (Scheme 11).^{16,17b}

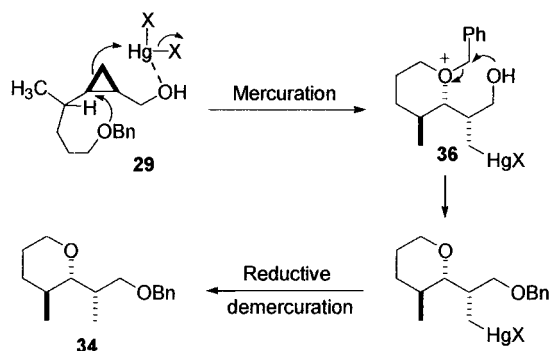
These reactions nicely complement the related electrophile-mediated cyclofunctionalizations of alkenes, or intramolecular ring-opening of epoxides for the synthesis of oxygen heterocycles.³¹ Whereas the intramolecular oxymercuration of alkenes or related unsaturated compounds have been used to synthesize oxygen heterocycles and especially those encountered in some naturally occurring ionophores,³² the corresponding reaction with cyclopropanes has received much less attention to our knowledge in the context of natural product synthesis. To further demonstrate the synthetic utility of these mercury-mediated cyclizations, the formation of heterocyclic compounds starting from several cyclopropanemethanol derivatives bearing at least one adjacent stereocenter

Table 2

Substrates	a,b	Oxygen heterocycles	Yield
			66%
			65%
			60%
			44%
			84%

^a Hg(OCOCF₃)₂, CH₂Cl₂, rt, then aq KBr. ^b *n*-Bu₃SnH, cat AIBN, THF.

Scheme 12

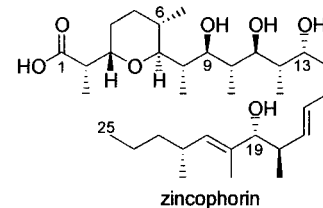
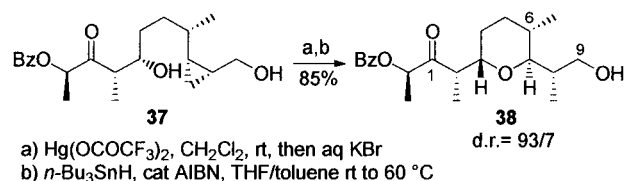


substituted by a methyl group and a remote nucleophilic moiety was investigated. The results are listed in Table 2.³⁰

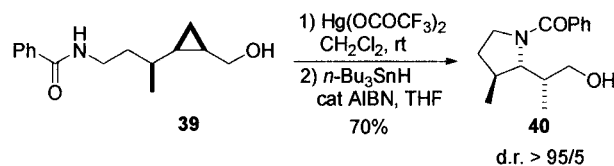
As anticipated, lactones **31** and **32** and tetrahydropyrans **33**–**35** could be synthesized from cyclopropanemethanols **26**–**30** (or their benzyl ethers) possessing appropriately located ester or hydroxy groups. A benzyl ether can also act as an internal nucleophile, as illustrated in the case of compound **29**, and is transferred to the remaining hydroxyl group of the final product **34** during the oxymercuration process, presumably from the intermediate oxonium species **36** (Scheme 12).³⁰

Finally, the mercury(II)-mediated cyclization can be applied to densely functionalized substrates such as **30**, with an hydroxyl group of a potentially sensitive aldol-type compound acting as the internal nucleophile. The corresponding tetrahydropyran **35** was obtained in excellent yield (84%) and with high diastereoselectivity (d.r.

Scheme 13



Scheme 14



> 96/4). The other carbonyl groups in compound **30**, which offer potential ligation sites for the mercury cation, did not interfere with the intramolecular oxymercuration (Table 2).

An intramolecular oxymercuration of the highly functionalized cyclopropanemethanol **37** has been used as a key step for the elaboration of the C₁–C₉ subunit in our total synthesis of the ionophore antibiotic zincophorin. The resulting tetrahydropyran **38** was obtained in excellent yield (85%) and with a satisfactory level of diastereoselectivity (d.r. ≥ 93/7) (Scheme 13).³³

Interestingly, these processes are not restricted to oxygen nucleophiles since the nitrogen atom of the amide group of the cyclopropane **39** could be used in order to elaborate the pyrrolidine **40** (70%). Worthy of note is the fact that this intramolecular aminomercuration proceeded with high regioselectivity favoring the formation of a five-membered ring at the expense of a six-membered ring, as an obvious consequence of the electronic bias provided by the cyclopropanemethanol (Scheme 14).³⁰

Conclusion

The regioselective electrophilic ring-opening of cyclopropylcarbinol derivatives mediated by mercury(II) salts with concomitant attack of an internal nucleophile provides a useful strategy for the stereoselective elaboration of acyclic structures bearing several contiguous stereocenters, as well as heterocycles. Although the use of mercury salts limits the development of these reactions to academic research activities, the results presented in this account should encourage the search for alternative mediators to effect these transformations. The scope of the electrophilic ring-opening of cyclopropanes mediated by mercury(II) salts has been further expanded through the course of these studies, by considering the case of cyclopropanemethanol derivatives bearing an adjacent methyl substituted

stereocenter for which efficient stereoselective syntheses have been devised. The potential application to complex natural product synthesis has also been highlighted with the elaboration of the C₁–C₉ subunit of zincophorin relying on an intramolecular oxymercuration of a cyclopropanemethanol as a key step.

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