JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

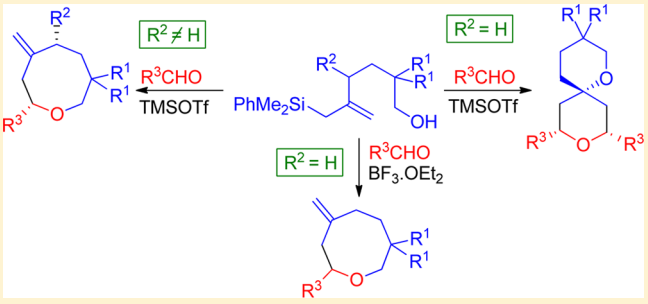
From Silylated Trishomoallylic Alcohols to Dioxaspiroundecanes or Oxocanes: Catalyst and Substitution Influence

Asunción Barbero,* Alberto Diez-Varga, Manuel Herrero, and Francisco J. Pulido

Departamento de Química Orgánica, Facultad de Ciencias, Campus Miguel Delibes, 47011 Valladolid, Spain

Supporting Information

ABSTRACT: A versatile method for the synthesis of dioxaspiroundecanes through a tandem Sakurai–Prins cyclization of allylsilyl alcohols in the presence of TMSOTf is described. The process is general and highly stereoselective with total control in the creation of three new stereogenic centers in a single step. Moreover, a very interesting chemoselectivity has been observed depending on the nature of the catalyst used or the substitution of the trishomoallylic alcohol, since the same reaction under $BF_3{\cdot}OEt_2$ catalysis or using alcohols with allylic substituents provides exclusively the corresponding oxocanes, by a direct silyl-Prins cyclization.



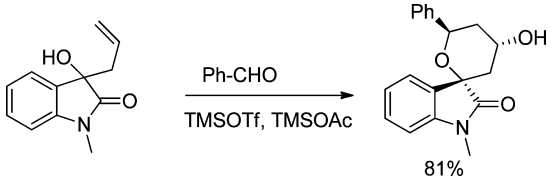
INTRODUCTION

Prins cyclization is one of the most efficient methods for the synthesis of different sized heterocycles. The reaction involves the intramolecular acid-catalyzed condensation of an alkenyl alcohol with an aldehyde to provide an oxocarbenium ion which is then trapped in situ by the alkenyl moiety to form the heterocyclic system.

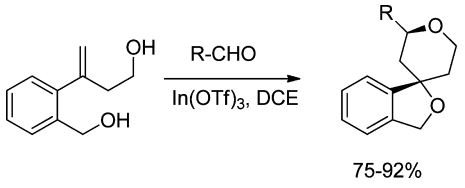
Although Prins-cyclization has been extensively used for the synthesis of common ring heterocycles[2] (mainly 5- and 6-membered rings), less frequent are the examples described for the preparation of spirodiheterocycles by means of a Prins reaction.[3] Essentially, two major strategies have been employed for the synthesis of these bicyclic systems: one of them involves the Prins-cyclization on a heterocyclic precursor that bears an alkenyl group and an alcohol. For instance, Damera and Wang[4] have used this protocol for the synthesis of spirooxindole pyrans through a Lewis acid promoted Prins cyclization (Scheme 1).

Another approach is based in a Prins cyclization of an acyclic trifunctional precursor which bears two nucleophilic components (a π-nucleophile and a hydroxy or amino group) and an electrophilic component (generally a hydroxy or amino group which would provide the oxocarbenium or iminium intermediate).[5] In one example of this methodology Reddy has reported an approach toward the synthesis of spiroisobenzofuran-pyran derivatives by means of a Prins cyclization of an alkenediol (Scheme 2).[6]

Scheme 1. Synthesis of Spirooxindole Pyrans by Prins Cyclization



Scheme 2. Synthesis of Spiroisobenzofuran-Pyrans by Prins Cyclization



The reaction involves the formation of the oxocarbenium ion by condensation of the allylic alcohol with the aldehyde, followed by 6-*endo* cyclization to give a tetrahydropyranyl cation, which is then intramolecularly trapped by the second hydroxy group.

As part of our interest for the synthesis of different sized carbo-[7,8] and heterocycles[9,10] using the chemistry of organosilanes, we have recently reported an approach to the synthesis of dioxaspirodecanes by means of a multicomponent Sakurai–Prins reaction of a bishomoallylic alcohol with an aldehyde. As far as we know, this has been the first reported synthesis of spirodiheterocycles from a difunctional precursor with a nucleophilic and an electrophilic components. Moreover, spiroheterocycles are rigid structures with activity in the field of medicine and agriculture. Thus, some of the several natural limonoids containing such substructure are Ivorenoid F,[11] which shows moderate activity against HL-60 cell line,

Received: September 28, 2015
Published: March 7, 2016

DOI: 10.1021/acs.joc.5b02260
J. Org. Chem. 2016, 81, 2704–2712

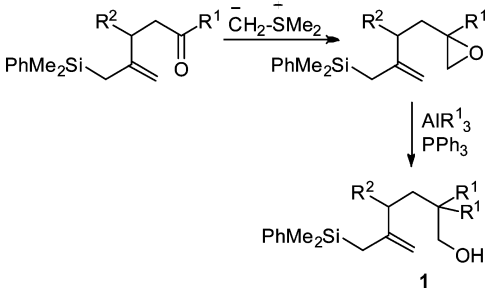
Cipanoid A,[12] isolated from the leaves of *Cipadessa cinerasecns* or Sandoripins A and B,[13] which show moderate inhibition toward nitric oxide production in mouse macrophage cell line J774.

We herein present an extension of this work where we have been able to prepare either dioxaspiroundecanes or oxocanes depending on the substitution of the starting material and the nature of the catalyst.

RESULTS AND DISCUSSION

The starting allylsilyl alcohols were obtained in three steps, such as silylcupration of allene to give allylsilyl ketones,[14] followed by epoxidation of the carbonyl group to provide the epoxide derivatives and final addition of an organoaluminum reagent[15] to obtain the needed primary alcohols. Unfortunately, allylsilyl alcohols **1** were unstable under chromatography conditions,[16] which made necessary to perform the following Prins cyclization without previous purification (Scheme 3).

Scheme 3. Obtention of Allylsilyl Alcohols 1



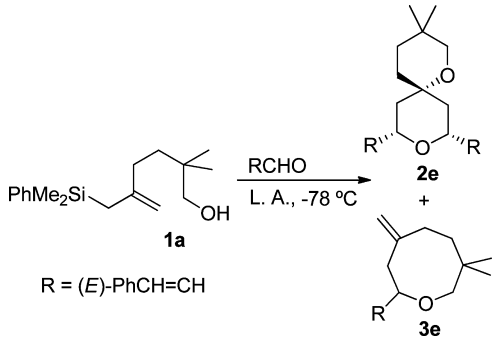
We choose alcohol **1a** as a model substrate to study the optimization of the cyclization process. Thus, reaction of **1a** (1 mmol) with cinnamaldehyde (2.2 mmol) at −78 °C, using TMSOTf (1.2 mmol) as catalyst, provided dioxaspiroundecane **2e** in 69% by means of a multicomponent Sakurai−Prins cyclization. None of the oxocane derivative **3e**, corresponding to a direct silyl-Prins cyclization, could be detected in the reaction mixture by ^{1}H or ^{13}C NMR spectroscopy. We then performed the same reaction studying the effect of different catalysts and conditions. The results are shownin Table 1.

As shown in Table 1, the same selectivity toward dioxaspiroundecane **2** was obtained using different amounts of TMSOTf (either 2.4 or 0.8 equiv), although yields slightly decreased. When $EtAlCl_2$ was used as catalyst a complex mixture was obtained where we could not detect any known compound. Surprisingly, the reaction in the presence of $BF_3{\cdot}OEt_2$ gave selectively a new compound which was shown to be oxocane **3e**.

We then evaluated the utility of the reaction for the obtention of dioxaspiroundecanes, using different allylsilyl alcohols and aldehydes under the optimized reaction conditions (Table 1, entry 2). The results are shown in Table 2.

As shown in Table 2, the reaction is general both for arylic and vinylic aldehydes[17] with good yields over two steps. The process is almost instantaneous, with reaction times ranging from 5 to 15 min. The reaction is highly chemoselective leading to the corresponding dioxaspiroundecanes **2**. The only example in which a small amount of the oxocane derivative **3b** was obtained, in addition to **2b**, is in the reaction with anisaldehyde (Table 2, entry 2). Moreover, the reaction is very stereoselective providing a single diastereoisomer. The relative stereochemistry of dioxaspiroundecanes **2** was confirmed by ^{1}H NMR and NOE experiments.

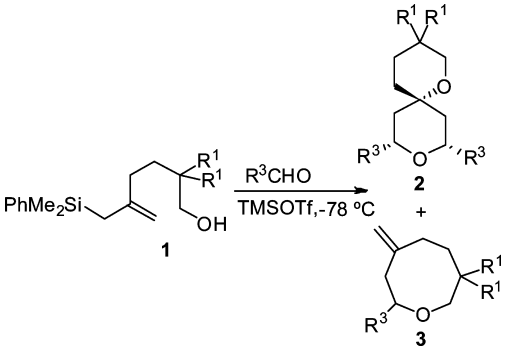
Table 1. Optimization of the Prins Cyclization



entry	catalyst	Lewis Acid equiv	ratio **2e**/**3e**	product[a] (yield, %)
1	TMSOTf	0.8	>95:5	**2e** (39)
2	TMSOTf	1.2	>95:5	**2e** (69)
3	TMSOTf	2.4	>95:5	**2e** (46)
4	$EtAlCl_2$	1.2		complex mixture
5	$BF_3{\cdot}OEt_2$	1.2	<5:95	**3e** (85)

[a]Conditions: **1a** (1.0 mmol), cinnamaldehyde (2.2 mmol), CH_2Cl_2.

Table 2. Scope of the Prins Cyclization of Allylsilyl Alcohols



entry	R^1	R^3	allylsilyl alcohol	ratio[a] **2**/**3**	product[b] (yield, %)
1	Me	C_6H_5	**1a**	>95:5	**2a** (59)
2	Me	4-$MeOC_6H_4$	**1a**	86:14	**2b**+**3b** (67)[c]
3	Me	4-MeC_6H_4	**1a**	>95:5	**2c** (54)
4	Me	4-ClC_6H_4	**1a**	>95:5	**2d** (49)
5	Me	(*E*)-PhCH=CH	**1a**	>95:5	**2e** (69)
6	Me	(*E*)-MeCH=CH	**1a**	>95:5	**2f** (65)
7	Et	4-MeC_6H_4	**1b**	>95:5	**2g** (49)
8	Et	(*E*)-PhCH=CH	**1b**	>95:5	**2h** (55)
9	Et	(*E*)-MeCH=CH	**1b**	>95:5	**2i** (48)

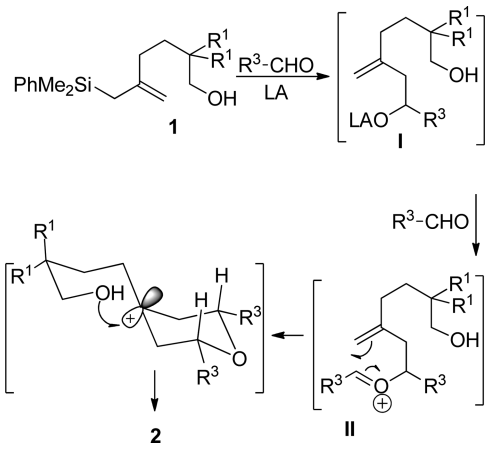
[a]The ratio of products was determined by ^{1}H NMR (400 MHz). [b]Conditions: **1** (1.0 mmol), aldehyde (2.2 mmol), TMSOTf (1.2 mmol), at −78 °C in CH_2Cl_2. [c]Occasionally we isolated in this reaction a minor byproduct, which showed to be tetrahydro-2,6-bis(4-methoxyphenyl)-4-(3-methylbut-3-enylidene)-2*H*-pyran **4b**.

A mechanistical proposal for the obtention of compounds **2** could be as follows. Allylsilyl alcohol **1** will undergo an acid catalyzed Sakurai reaction with 1 equiv of aldehyde to afford a homoallylic alkoxide intermediate **I**. Subsequent reaction of **I** with a second equiv of aldehyde will lead to an oxocarbenium ion **II**, which will undergo intramolecular attack of the alkene

DOI: 10.1021/acs.joc.5b02260
J. Org. Chem. 2016, 81, 2704−2712

moiety to give a tertiary tetrahydropyranyl cation. The intramolecular capture of the cationic intermediate by the primary alcohol will finally provide the shown dioxaspirobicycle **2** (Scheme 4).

Scheme 4. Mechanism of the Tandem Sakurai–Prins Cyclization



In this tandem reaction three stereogenic centers are introduced in one step with total stereocontrol. The high stereocontrol observed in this tandem cyclization may be rationalized by a favored chairlike transition state in which the bulkier groups (R^3) adopt an equatorial conformation for minimal repulsions (Scheme 4).

Conclusive evidence for this mechanism pathway can be found in the obtention of tetrahydropyran **4b**,[18] as an occasional byproduct of the reaction of **1a** with anisaldehyde. The formation of **4b** could be explained by a Sakurai reaction of intermediate **5** (presumably obtained by deoxygenation of the corresponding epoxide in the presence of PPh_3,[19] Scheme 3), with *p*-anisaldehyde to give a homoallylic alkoxide **III**. Subsequent reaction of **III** with another equiv of *p*-anisaldehyde will provide the shown oxocarbenium ion, which will further undergo Prins cyclization to give a tetrahydropyranyl cation. The final deprotonation step will afford methylenetetrahydropyran **4b** (Scheme 5).

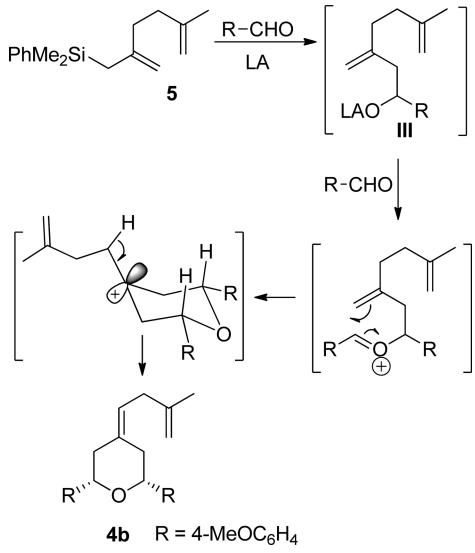
Influence of the Catalyst. We then decided to study further the different chemical behavior observed for the reaction of allylsilyl alcohol **1a** with cinnamaldehyde under different Lewis acids (Table 1, entries 2 and 5). As shown in Table 1, while the reaction in the presence of TMSOTf selectively gives dioxaspiroundecane **2e**, when $BF_3{\cdot}OEt_2$ is used as catalyst oxocane **3e** is exclusively obtained in good yield. This reaction is remarkable since there have been very few examples reported on the synthesis of medium sized oxacycles using Prins cyclization.[20]

Encouraged by this interesting chemoselectivity, we explored the reaction with $BF_3{\cdot}OEt_2$ using other aldehydes. The results are shown in Scheme 6.

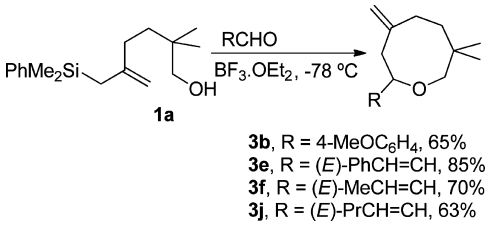
As shown in Scheme 6, allylsilyl alcohol **1a** reacts efficiently with aldehydes in the presence of $BF_3{\cdot}OEt_2$ to give oxocanes **3** in good yields and with excellent chemoselectivity (none of the corresponding dioxaspiroundecanes **2** were found in the reaction mixture). The reaction is general both for arylic and vinylic aldehydes.[21]

The effect of the catalyst on the chemoselectivity of the reaction remains to be rationalized. The final outcome of the reaction will be determined by which of the two processes is the most favorable (the initial Sakurai reaction to generate the intermediate homoallylic alkoxide **I** (Scheme 4) or the direct silyl-Prins cyclization leading to the oxocane derivative). A wide variety of Lewis Acids (TMSOTf, Et_2AlCl, $SnCl_4$, $InCl_3$, etc.) has shown to be efficient promoting the silyl-Prins cyclization.[2] Although less frequent, $BF_3{\cdot}OEt_2$ has also been used in these cyclizations with good results.[22] On the other hand, the Sakurai reaction of allylsilanes with aldehydes promoted by $BF_3{\cdot}OEt_2$ has also been reported.[23] Bottoni and Tagliavini[24] have postulated that this reaction proceeds through an eight-membered transition state in which an incipient Si–F bond is formed. Regarding the reactions of our allylsilyl alcohol **1a** with aldehydes in the presence of $BF_3{\cdot}OEt_2$ leading to oxocanes (Scheme 6), we now presume that the corresponding eight-membered TS needed for the Sakurai reaction, which would be the initial step of the tandem process leading to dioxaspiroundecanes, is not favored due to steric hindrance. However, further studies have to be conducted in order to gain insight into these reactions.

Scheme 5. Mechanism for the Formation of 4b



Scheme 6. Reaction of Allylsilyl Alcohols under $BF_3{\cdot}OEt_2$ Catalysis Leading to Oxocanes

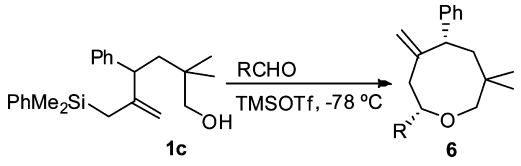


Influence of the Substitution on the Trishomoallylic Alcohol. Finally, we examined the influence of the substitution in the outcome of the process. For that purpose we choose a trishomoallylic alcohol that bears an allylic substituent such as **1c**. To our surprise the reaction of alcohol **1c** with aldehydes under TMSOTf catalysis did not afford the corresponding dioxaspiroundecane but oxocanes **6** in a very efficient manner. The results are shown in Table 3.

As shown, the cyclization proceeds in high yield and with excellent stereocontrol to afford *cis*-2,5-disubstituted oxocanes.

DOI: 10.1021/acs.joc.5b02260
J. Org. Chem. 2016, 81, 2704–2712

Table 3. Scope of the Silyl-Prins Cyclization of Allylsilyl Alcohol 1c



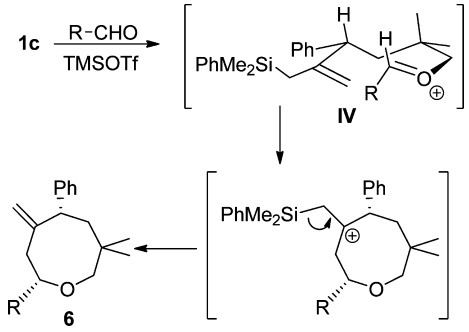
entry	R	TMSOTf equiv	ratio[a] 6	product[b] (yield, %)
1	Ph	1.2	>95:5	**6a** (82)
2	4-MeOPh	1.2	>95:5	**6b** (83)
3	4-MePh	1.2	>95:5	**6c** (80)
4	4-ClPh	1.2	>95:5	**6d** (81)
5	CH2=CH	1.2	>95:5	**6e** (70)
6	(*E*)-PhCH=CH	1.2	>95:5	**6f** (83)
7	(*E*)-MeCH=CH	1.2	>95:5	**6g** (82)
8	(*E*)-^{n}PrCH=CH	1.2	>95:5	**6h** (75)
9	(*E*)-^{i}BuCH=CPh	1.2	>95:5	**6i** (71)

[a]None of the corresponding *trans*-2,5-disubstituted oxocanes could be detected in the reaction mixture by ^{1}H NMR (400 MHz). [b]Conditions: **1c** (1.0 mmol), aldehyde (1.2 mmol) at −78 °C in CH_2Cl_2.

The reaction works well both for aromatic aldehydes (with electron donating or electron withdrawing susbstituents) and vinylic aldehydes. The structure and stereochemistry of compounds **6a**−**6i** were established on the basis of ^{1}H NMR and NOE experiments.

The formation of oxocanes **6** may be explained through a direct silyl-Prins cyclization as indicated in Scheme 7. The

Scheme 7. Mechanism of the Direct Silyl-Prins Cyclization

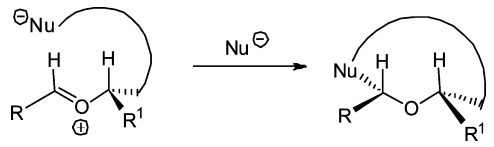


general mechanism for this reaction implies the formation of a preferred *E*-oxocarbenium ion **IV**, by the acid catalyzed reaction of the hydroxyl group with the aldehyde, followed by 8-*endo* cyclization to afford an oxecanyl cation. Subsequent loss of the silyl group will provide the oxocane derivative **6** (Scheme 7).

The stereochemical outcome of this reaction can be explained by a preferred transition state where the substituents adopt a pseudoequatorial conformation to avoid unfavorable steric interactions.

As known, the preferred geometry of the intermediate oxocarbenium ion will determine the final stereochemical outcome of Prins cyclization. Houk's computational studies[25] show that the *trans*-isomer of oxocarbenium ions are more stable than the *cis*. This is consistent with a favored conformation in which the alkyl−alkyl steric interactions showed in the *cis* isomer are avoided. Moreover, calculations also predict that nucleophilic attack on an oxocarbenium ion, that bears an α-stereocenter, occurs from the less hindered face of the double bond, in a conformation in which the smallest substituent on the stereogenic center is coplanar with the C=O^{+} bond. (Scheme 8). However, the presence in the

Scheme 8. Houk's Prediction on the Stereofacial Attack of Nucleophiles to Oxocarbenium Ions

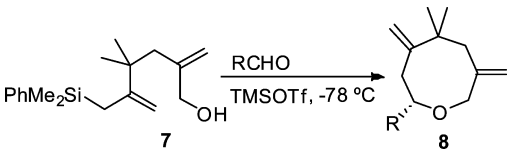


molecule of another stereogenic center remote from the oxocarbenium ion does not always produce the same stereocontrol, as we have recently reported.[10b] To our delight, in this case the obtention of *cis*-2,5-oxocanes is completely stereoselective.

We then decided to use an alcohol with allylic substituents but having the stereogenic center at a different position. To prepare the needed 2-monosubstituted alcohol we used Lewinski's conditions[26] for the *anti*-Markovnikov reductive opening of epoxides. To our surprise, we did not get the expected 5-dimethylphenylsilylmethyl-2,4,4-trimethylhex-5-en-1-ol, but alcohol **7** due to an elimination process.[27] Unfortunately alcohol **7** was unstable under chromatography, what led us to use it without further purification.

Although unexpected, this result is even more interesting since we have incorporated a functional group in the starting material which could be used for the appropriate transformation in the oxocanyl ring. In fact, many natural oxocanes such as Laurencin,[28] laurenyne[29] or *cis*-dihydrorhodophytin,[30] which are secondary metabolites isolated from the red algae genus Laurencia with antimicrobial, insecticidal or cytotoxic activities, are halogenated at C-3 and the location of an exocyclic double bond at that position seems to be most convenient. The reaction of **7** with aldehydes under TMSOTf catalysis provided the corresponding 3-functionalyzed oxocanes **8** with good yields over two steps (Table 4).

Table 4. Synthesis of 3-Functionalyzed Oxocanes



entry	R	TMSOTf equiv	product[a] (yield, %)
1	Ph	1.2	**8a** (52)
2	4-MeOPh	1.2	**8b** (55)
3	(*E*)-PhCH=CH	1.2	**8c** (51)
4	(*E*)-MeCH=CH	1.2	**8d** (59)
5	(*E*)-^{n}PrCH=CH	1.2	**8e** (57)

[a]Conditions: **7** (1.0 mmol), aldehyde (1.2 mmol), CH_2Cl_2.

Hence, two different reaction pathways are possible in the reaction of trishomoallylic alcohols with aldehydes in the presence of TMSOTf. Thus, alcohols bearing allylic substituents selectively undergo the direct Prins cyclization leading to oxocane derivatives. On the other hand, under the same conditions trishomoallylic alcohols lacking allylic substituents give dioxaspiroundecanes through a tandem Sakurai−Prins reaction. The reason for this chemoselectivity dependence on

DOI: 10.1021/acs.joc.5b02260
J. Org. Chem. 2016, 81, 2704−2712

the substitution of the starting alcohol remains unknown although some steric factors may account for it. As we have previously reported,[10b] our hypothesis is that the initial Sakurai reaction leading to dioxaspiroundecanes is severely disfavored by the allylic substituent in allylsilyl alcohols **1c** or **7**. As known, the hyperconjugative stabilization in β-silyl carbocations requires a parallel alignment between the Si−Cα bond and the empty p orbital, what would force the incoming electrophile to attack *anti* to the silyl group. We now pressume that in such conformation the allylic substituent of allylsilanes **1c** and **7** is blocking the approach of the aldehyde, what would explain why allylsilyl alcohols with allylic substituents selectively undergo direct silyl-Prins cyclization instead of the tandem Sakurai−Prins reaction.

CONCLUSION

In conclusion, we have reported an efficient synthesis of oxocanes and dioxaspiroundecanes starting from trishomoallylic alcohols. The reaction leading to dioxaspiroundecanes involves a tandem Sakurai−Prins reaction while oxocanes are obtained by a direct Prins-cyclization. Interestingly, the chemoselectivity of this reaction is dependent on the catalyst used and the substitution of the trishomoallylic alcohol.

EXPERIMENTAL SECTION

General Procedures. All reagents were purchased from commercial suppliers as reagent grade and used without further purification, unless otherwise stated. Tetrahydrofuran and dichloromethane were dried by standard methods (dichloromethane was distilled from CaH_2, tetrahydrofuran was dried with preactivated molecular sieves (3 Å). All reactions were conducted in flame-dried glassware under nitrogen atmosphere, except where otherwise noted. Yields refer to chromatographically pure compounds, unless otherwise stated.

Flash column chromatography was performed using Silica Gel 60 (230−400 mesh ASTM). TLC was done under aluminum backed plate, precoated with silica gel (0.20 mm, silica gel 60) with a fluorescent indicator (254 nm).

Melting points were obtained on an electrothermal melting point apparatus and are uncorrected.

NMR spectra were recorded at 400 MHz (^{1}H, 400.123 MHz; ^{13}C, 100.611 MHz) and 500 MHz (^{1}H, 400.123 MHz; ^{13}C, 100.611 MHz) at room temperature (25 °C). Chemical shifts (δ) were reported in parts per million (ppm) relative to the residual solvent peaks recorded, rounded to the nearest 0.01 for ^{1}H NMR and 0.1 for ^{13}C NMR (reference: $CDCl_3$ [^{1}H: 7.26, ^{13}C: 77.2]). The ^{13}C NMR was recordered with complete proton decoupling. Carbon types, structure assignments and attribution of peaks were determined from DEPT-NMR and two-dimensional correlation experiments (HMQC (^{1}H−^{13}C), COSY (^{1}H−^{1}H) and HMBC (^{1}H−^{13}C). Relative stereochemistry was assigned based on the 1D-NOE experiments, considering the signals corresponding to the interactions highlighted in the spectra. High-resolution mass spectra (HRMS) were measured on a UPLC-MS system by electrospray ionization (ESI positive and negative) using a QTOF mass analyzer.

Compounds **1a−c** were prepared in three steps such as silylcupration of allene and reaction with α,β-unsaturated ketones, formation of the epoxide using sulfur ylides and obtention of the primary alcohol by reaction of the epoxide with R_3Al under Scheider's conditions.[14] Compound **7** (4,4-dimethyl-5-phenyldimethylsilylmethyl-2-methylenehex-5-en-1-ol) was prepared from the corresponding 2,4,4-trimethyl-5-phenyldimethylsilylmethyl-1,2,-epoxy-5-hexene[14] by reaction with ^{i}Bu$_3$Al.[26]

Typical Procedure for the Obtention of Dioxaspiroundecanes 2. TMSOTf (1.2 mmol) was added dropwise to a stirred solution of allylsilyl alcohols **1a,b** (1 mmol) and the aldehyde (2.2 mmol) in dry CH_2Cl_2 (13 mL) at −78 °C, under nitrogen. The reaction mixture was stirred for 10−15 min at −78 °C. Aqueous NaOH (2 mL) was added, the mixture was extracted with diethyl ether, and the combined organic layers were dried and concentrated to dryness. The product was isolated by column chromatography on silica gel (eluent = hexanes/ethyl acetate) to afford the corresponding products.

*3,3-Dimethyl-8,10-diphenyl-1,9-dioxaspiro[5.5]undecane (**2a**).* The product was isolated as a yellow solid (recrystallized from hexane); mp 69.2−69.4 °C (198 mg, 59% yield) using flash chromatography 20:1 hexane/EtOAc (R_f = 0.34, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 7.8 Hz, 4H), 7.38−7.33 (m, 4H), 7.30−7.26 (m, 2H), 4.61 (d, J = 11.4 Hz, 2H), 3.33 (s, 2H), 2.22 (d, J = 13.0 Hz, 2H), 1.99−1.94 (m, 2H), 1.72 (dd, J = 13.0 and 11.4 Hz, 2H), 1.56−1.52 (m, 2H), 0.96 (s, 6H;. ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6 (C), 128.5 (CH), 127.7 (CH), 126.2 (CH), 76.9 (CH), 71.9 (C), 71.0 (CH_2), 43.7 (CH_2), 32.8 (CH_2), 30.1 (C), 27.9 (CH_2), 25.5 (CH_3); HRMS (ESI+) m/z calcd for $C_{23}H_{28}NaO_2$ ([M + Na]$^+$): 359.1982, found 359.1982.

*3,3-Dimethyl-8,10-di(4-methoxyphenyl)-1,9-dioxa-spiro[5.5]-undecane (**2b**).* The product was isolated as a white solid (recrystallized from hexane); mp 123.0−123.2 °C (230 mg, 58% yield) using flash chromatography 8:1 hexane/EtOAc (R_f = 0.18, 10:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 4H), 6.87 (d, J = 8.7 Hz, 4H), 4.53 (d, J = 11.6 Hz, 2H), 3.79 (s, 6H), 3.32 (s, 2H), 2.16 (d, J = 13.0 Hz, 2H), 1.96−1.90 (m, 2H), 1.70 (dd, J = 13.0 and 11.6 Hz, 2H), 1.52−1.49 (m, 2H), 0.94 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C), 134.9 (C), 127.6 (CH), 113.9 (CH), 76.5 (CH), 71.9 (C) 71.1 (CH_2), 55.5 (CH_3), 43.6 (CH_2), 32.8 (CH_2), 30.1 (C), 27.9 (CH_2), 25.5 (CH_3); HRMS (ESI+) m/z calcd for $C_{25}H_{33}O_4$ ([M + H]$^+$): 397.2378, found 397.2373 m/z calcd for $C_{25}H_{32}NaO_4$ ([M + Na]$^+$): 419.2195, found 419.2193.

*Tetrahydro-2,6-bis(4-methoxyphenyl)-4-(3-methylbut-3-enylidene)-2H-pyran (**4b**).* The product was isolated as a viscous yellow oil using flash chromatography 8:1 hexane/EtOAc (R_f = 0.34, 10:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.36 (m, 4H), 6.91−6.87 (m, 4H), 5.40 (t, J = 7.4 Hz, 1H), 4.76 (s, 2H), 4.48 (dd, J = 8.7 and 5.1 Hz, 1H), 4.41 (dd, J = 11.4 and 2.3 Hz, 1H), 3.80 (s, 6H), 2.80−2.75 (m, 2H), 2.42−2.36 (m, 2H), 2.15−2.09 (m, 1H), 2.09−2.03 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (C), 159.1 (C), 145.1 (C), 136.2 (C), 135.2 (C), 135.1 (C), 127.4 (CH), 127.3 (CH), 121.5 (CH), 113.9 (CH), 113.8 (CH), 110.4 (CH_2), 80.8 (CH), 80.0 (CH), 55.5 (CH_3), 55.4 (CH_3), 44.5 (CH_2), 37.2 (CH_2), 35.7 (CH_2), 22.8 (CH_3); HRMS (ESI+) m/z calcd for $C_{24}H_{29}O_3$ ([M + H]$^+$): 365.2115, found 365.2111 m/z calcd for $C_{24}H_{28}NaO_3$ ([M + Na]$^+$): 387.1932, found 387.1931.

*3,3-Dimethyl-8,10-di(4-methylphenyl)-1,9-dioxa-spiro[5.5]-undecane (**2c**).* The product was isolated as a viscous yellow oil (197 mg, 54% yield) using flash chromatography 20:1 hexane/EtOAc (R_f = 0.38, 15:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 7.9 Hz, 4H), 7.16 (d, J = 7.9 Hz, 4H), 4.56 (d, J = 11.6 Hz, 2H), 3.32 (s, 2H), 2.34 (s, 6H), 2.19 (d, J = 12.8 Hz, 2H), 1.97−1.92 (m, 2H), 1.71 (dd, J = 12.8 and 11.6 Hz, 2H), 1.54−1.50 (m, 2H), 0.95 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (C), 137.2 (C), 129.1 (CH), 126.2 (CH), 76.7 (CH), 71.9 (C), 71.0 (CH_2), 43.7 (CH_2), 32.8 (CH_2), 30.1 (C), 27.9 (CH_2), 25.5 (CH_3), 21.3 (CH_3); HRMS (ESI+) m/z calcd for $C_{25}H_{33}O_2$ ([M + H]$^+$): 365.2471, found 365.2475 m/z calcd for $C_{25}H_{32}NaO_2$ ([M + Na]$^+$): 387.2295, found 387.2295.

*3,3-Dimethyl-8,10-di(4-chlorophenyl)-1,9-dioxa-spiro[5.5]-undecane (**2d**).* The product was isolated as a yellow solid (recrystallized from hexane); mp 114.6−114.8 °C (198 mg, 49% yield) using flash chromatography 20:1 hexane/EtOAc (R_f = 0.29, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 8H), 4.56 (d, J = 12.0 Hz, 2H), 3.31 (s, 2H), 2.18 (d, J = 13.1 Hz, 2H), 1.95−1.89 (m, 2H), 1.68−1.60 (m, 2H), 1.54−1.49 (m, 2H), 0.95 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9 (C), 133.4 (C), 128.7 (CH), 127.5 (CH), 76.3 (CH), 71.6 (C), 71.1 (CH_2), 43.6 (CH_2), 32.8 (CH_2), 29.5 (C), 27.9 (CH_2), 25.5 (CH_3); HRMS (ESI+) m/z calcd for $C_{23}H_{27}Cl_2O_2$ ([M + H]$^+$): 405.1383, found 405.1384 m/z calcd for $C_{23}H_{26}Cl_2NaO_2$ ([M + Na]$^+$): 427.1202, found 427.1200.

DOI: 10.1021/acs.joc.5b02260
J. Org. Chem. 2016, 81, 2704−2712

*3,3-Dimethyl-8,10-distyryl-1,9-dioxa-spiro[5.5]undecane (**2e**).* The product was isolated as a yellow solid (recrystallized from hexane); mp 40.2−40.4 °C (268 mg, 69% yield) using flash chromatography 20:1 hexane/EtOAc (R_f = 0.25, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.38 (m, 4H), 7.34−7.29 (m, 4H), 7.26−7.21 (m, 2H), 6.66 (d, J = 16.0 Hz, 2H), 6.27 (dd, J = 16.0 and 6.3 Hz, 2H), 4.18 (dd, J = 11.4 and 6.3 Hz, 2H), 3.35 (s, 2H), 2.09 (d, J = 12.7 Hz, 2H), 1.86−1.80 (m, 2H), 1.60−1.47 (m, 4H), 0.96 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (C), 131.0 (CH), 129.9 (CH), 128.6 (CH), 127.8 (CH), 126.7 (CH), 75.0 (CH), 71.4 (C), 71.1 (CH_2), 41.5 (CH_2), 32.8 (CH_2), 30.1 (C), 28.0 (CH_2), 25.5 (CH_3); HRMS (ESI+) m/z calcd for $C_{27}H_{33}O_2$ ([M + H]$^+$): 389.2476, found 389.2475 m/z calcd for $C_{27}H_{32}NaO_2$ ([M + Na]$^+$): 411.2296, found 411.2295.

*3,3-Dimethyl-8,10-di((E)-prop-1-enyl)-1,9-dioxa-spiro[5.5]-undecane (**2f**).* The product was isolated as a yellow oil (172 mg, 65% yield) using flash chromatography 20:1 hexane/EtOAc (R_f = 0.28, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (dq, J = 15.4 and 6.4 Hz, 2H), 5.50 (ddd, J = 15.4, 6.8, and 0.9 Hz, 2H), 3.84 (dd, J = 11.3 and 6.8 Hz, 2H), 3.30 (s, 2H), 1.90 (d, J = 12.8 Hz, 2H), 1.73−1.66 (m, 8H), 1.43−1.33 (m, 4H), 0.91 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.9 (CH), 127.8 (CH), 74.9 (CH), 71.3 (C), 71.0 (CH_2), 41.4 (CH_2), 32.7 (CH_2), 30.0 (C), 27.9 (CH_2), 25.5 (CH_3), 17.9 (CH_3); HRMS (ESI+) m/z calcd for $C_{17}H_{29}O_2$ ([M + H]$^+$): 265.2156, found 265.2162 m/z calcd for $C_{17}H_{28}NaO_2$ ([M + Na]$^+$): 287.1980, found 287.1982.

*3,3-Diethyl-8,10-di(4-methylphenyl)-1,9-dioxa-spiro[5.5]-undecane (**2g**).* The product was isolated as a viscous yellow oil (192 mg, 49% yield) using flash chromatography 20:1 hexane/EtOAc (R_f = 0.40, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.14 (m, 8H), 4.55 (d, J = 12.2 Hz, 2H), 3.37 (s, 2H), 2.34 (s, 6H), 2.22−2.19 (m, 2H), 1.91−1.85 (m, 2H), 1.69 (dd, J = 12.8 and 12.2 Hz, 2H), 1.57−1.51 (m, 2H), 1.36−1.31 (m, 4H), 0.79 (t, J = 7.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (C), 137.1 (C), 129.0 (CH), 126.1 (CH), 76.7 (CH), 72.0 (C), 68.0 (CH_2), 43.8 (CH_2), 34.6 (C), 28.4 (CH_2), 27.3 (CH_2), 25.8 (CH_2), 21.2 (CH_3), 7.3 (CH_3); HRMS (ESI+) m/z calcd for $C_{27}H_{37}O_2$ ([M + H]$^+$): 393.2790, found 393.2788 m/z calcd for C27H36NaO2 ([M + Na]$^+$): 415.2612, found 415.2608.

*3,3-Diethyl-8,10-distyryl-1,9-dioxa-spiro[5.5]undecane (**2h**).* The product was isolated as a viscous yellow oil (229 mg, 55% yield) using flash chromatography 20:1 hexane/EtOAc (R_f = 0.24, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 10H), 6.64 (d, J = 16.0 Hz, 2H), 6.26 (dd, J = 16.0 and 6.2 Hz, 2H), 4.17 (dd, J = 11.7 and 6.2 Hz, 2H), 3.40 (s, 2H), 2.08 (d, J = 12.7 Hz, 2H), 1.81−1.76 (m, 2H), 1.57−1.48 (m, 4H), 1.38−1.31 (m, 4H), 0.80 (t, J = 7.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9 (C), 130.9 (CH), 129.9 (CH), 128.6 (CH), 127.7 (CH), 126.6 (CH), 75.0 (CH), 71.6 (C), 68.1 (CH_2), 41.7 (CH_2), 34.6 (C), 28.4 (CH_2), 27.4 (CH_2), 25.9 (CH_2), 7.4 (CH_3); HRMS (ESI+) m/z calcd for $C_{29}H_{37}O_2$ ([M + H]$^+$): 417.2787, found 417.2788 m/z calcd for $C_{29}H_{36}NaO_2$ ([M + Na]$^+$): 439.2607, found 439.2608.

*3,3-Diethyl-8,10-di((E)-prop-1-enyl)-1,9-dioxa-spiro[5.5]-undecane (**2i**).* The product was isolated as a yellow oil (140 mg, 48% yield) using flash chromatography 20:1 hexane/EtOAc (R_f = 0.29, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73−5.67 (m, 2H), 5.50 (dq, J = 15.3 and 6.7 Hz, 2H), 3.84 (dd, J = 11.3 and 7.0 Hz, 2H), 3.35 (s, 2H), 1.90 (d, J = 12.7 Hz, 2H), 1.68−1.62 (m, 8H), 1.43−1.26 (m, 8H), 0.77 (t, J = 7.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.3 (CH), 128.0 (CH), 75.2 (CH), 71.8 (C), 68.3 (CH_2), 41.9 (CH_2), 34.9 (C), 28.7 (CH_2), 27.7 (CH_2), 26.1 (CH_2), 18.2 (CH_3), 7.6 (CH_3); HRMS (ESI+) m/z calcd for $C_{19}H_{33}O_2$ ([M + H]$^+$): 293.2453, found 293.2475 m/z calcd for $C_{19}H_{32}NaO_2$ ([M + Na]$^+$): 315.2295, found 315.2295.

Typical Procedure for the Obtention of Oxocanes. TMSOTf or $BF_3{\cdot}OEt_2$ (1.2 mmol) was added dropwise to a stirred solution of the allylsilyl alcohols **1a,c** or **7** (1 mmol) and the aldehyde (1.2 mmol) in CH_2Cl_2 (13 mL) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C. Aqueous NaOH (2 mL) was added, the mixture was extracted with diethyl ether, and the combined organic layers were dried with $MgSO_4$ anhydrous and concentrated to dryness. The product was isolated by column chromatography on silica gel (eluent = hexanes/ethyl acetate) to afford the corresponding products.

*2-(4-Methoxyphenyl)-7,7-dimethyl-4-methyleneoxocane (**3b**).* The product was isolated as a yellow oil (169 mg, 65% yield) using flash chromatography 30:1 hexane/EtOAc (R_f = 0.46, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 6.87 (dd, J = 8.7 and 1.2 Hz, 2H), 4.95 (s, 1H), 4.87 (s, 1H), 4.46 (dd, J = 9.9 and 2.4 Hz, 1H), 3.80 (s, 3H), 3.57 (d, J = 11.7 Hz, 1H), 3.47 (d, J = 11.7 Hz, 1H), 2.50−2.40 (m, 3H), 2.33−2.27 (m, 1H), 2.19−2.11 (m, 1H), 1.24−1.19 (m, 1H), 1.01 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C), 149.6 (C), 136.4 (C), 127.2 (CH), 113.8 (CH), 112.7 (CH_2), 86.0 (CH), 78.2 (CH_2), 55.5 (CH_3), 44.3 (CH_2), 36.0 (C), 34.7 (CH_2), 33.5 (CH_2), 29.0 (CH_3), 22.6 (CH_3); HRMS (ESI+) m/z calcd for $C_{17}H_{25}O_2$ ([M + H]$^+$): 261.1847, found 261.1849 m/z calcd for $C_{17}H_{24}NaO_2$ ([M + Na]$^+$): 283.1664, found 283.1669.

*7,7-Dimethyl-2-(E)-styryl-4-methyleneoxocane (**3e**).* The product was isolated as a yellow oil (218 mg, 85% yield) using flash chromatography 50:1 hexane/EtOAc (R_f = 0.51, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.38 (m, 2H), 7.33−7.19 (m, 3H), 6.62 (d, J = 16.0 Hz, 1H), 6.28 (dd, J = 16.0 and 6.0 Hz, 1H), 4.94 (s, 1H), 4.86 (s, 1H), 4.21−4.13 (m, 1H), 3.48 (s, 2H), 2.51−2.41 (m, 2H), 2.34−2.26 (m, 2H), 2.05−1.96 (m, 1H), 1.30−1.23 (m, 1H), 0.99 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2 (C), 137.2 (C), 131.2 (CH), 129.8 (CH), 128.6 (CH), 127.5 (CH), 126.6 (CH), 112.7 (CH_2), 84.2 (CH), 77.7 (CH_2), 42.0 (CH_2), 35.8 (C), 35.0 (CH_2), 33.3 (CH_2), 28.6 (CH_3), 23.1 (CH_3); HRMS (ESI+) m/z calcd for $C_{18}H_{25}O$ ([M + H]$^+$): 257.1900, found 257.1900 m/z calcd for $C_{18}H_{24}NaO$ ([M + Na]$^+$): 279.1717, found 279.1719.

*7,7-Dimethyl-4-methylene-2-((E)-prop-1-enyl)oxocane (**3f**).* The product was isolated as a yellow oil (136 mg, 70% yield) using flash chromatography 30:1 hexane/EtOAc (R_f = 0.60, 15:1 hexane/EtOAc). Due to its low polarity some silicon subproducts could not be removed. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dqd, J = 15.3, 6.4, and 1.0 Hz, 1H), 5.57 (dd, J = 15.3 and 6.6 Hz, 1H), 4.90 (s, 1H), 4.80 (s, 1H), 3.96−3.90 (m, 1H), 3.42 (s, 2H), 2.45−2.38 (m, 1H), 2.36 (dd, J = 13.3 and 2.7 Hz, 1H), 2.29−2.24 (m, 1H), 2.20 (dd, J = 13.3 and 10.1 Hz, 1H), 2.05−1.95 (m, 1H), 1.71 (d, J = 6.4 Hz, 3H), 1.24−1.19 (m, 1H), 0.95 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6 (C), 133.0 (CH), 126.3 (CH), 112.4 (CH_2), 84.4 (CH), 77.6 (CH_2), 42.0 (CH_2), 35.7 (C), 35.1 (CH_2), 33.4 (CH_2), 28.6 (CH_3), 23.1 (CH_3), 17.9 (CH_3); HRMS (ESI+) m/z calcd for $C_{13}H_{23}O$ ([M + H]$^+$): 195.1741, found 195.1743.

*7,7-Dimethyl-4-methylene-2-((E)-pent-1-enyl)oxocane (**3j**).* The product was isolated as a yellow oil (140 mg, 63% yield) using flash chromatography 30:1 hexane/EtOAc (R_f = 0.70, 20:1 hexane/EtOAc). Due to its low polarity some silicon subproducts could not be removed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (dt, J = 15.5 and 6.4 Hz, 1H), 5.53 (dd, J = 15.5 and 6.3 Hz, 1H), 4.89 (s, 1H), 4.80 (s, 1H), 3.95−3.92 (m, 1H), 3.41 (s, 2H), 2.46−2.33 (m, 2H), 2.29−2.16 (m, 2H), 2.07−1.92 (m, 3H), 1.46−1.38 (m, 2H), 1.21 (ddd, J = 14.4, 5.8, and 2.8 Hz, 1H), 0.94 (s, 3H), 0.91 (t, J = 7.3 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5 (C), 131.7 (CH), 131.4 (CH), 112.4 (CH_2), 84.5 (CH), 77.5 (CH_2), 42.0 (CH_2), 35.7 (C), 34.8 (CH_2), 34.6 (CH_2), 33.4 (CH_2), 28.7 (CH_3), 23.0 (CH_3), 22.4 (CH_2), 13.9 (CH_3); HRMS (ESI+) m/z calcd for $C_{15}H_{26}NaO$ ([M + Na]$^+$): 245.1878, found 245.1876.

*rac-(2S,5R)-7,7-Dimethyl-4-methylene-2,5-diphenyl-oxocane (**6a**).* The product was isolated as a white solid (recrystallized from hexane); mp 78.3−78.5 °C (251 mg, 82% yield) using flash chromatography 25:1 hexane/EtOAc (R_f = 0.56, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.29 (m, 10H), 5.28 (s, 1H), 5.11 (s, 1H), 4.62 (dd, J = 10.7 and 2.3 Hz, 1H), 3.89 (d, d, J = 11.9 Hz, 1H), 3.85 (dd, (dd, J = 13.3 and 2.7 Hz, 1H), 3.60 (d, J = 11.9 Hz, 1H), 2.66 (dd, J = 14.2 and 13.3 Hz, 1H), 2.60−2.53 (m, 1H), 2.46−2.41 (m, 1H), 1.51 (dd, J = 14.2 and 2.1 Hz, 1H), 1.17 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (C), 145.9 (C), 143.8 (C), 128.4 (CH), 127.4 (CH), 127.1 (CH), 126.2 (CH), 125.9 (CH), 114.9 (CH_2), 86.7 (CH), 77.6 (CH_2), 48.5 (CH), 42.3

DOI: 10.1021/acs.joc.5b02260
J. Org. Chem. 2016, 81, 2704−2712

(CH_2), 39.6 (CH_2), 35.6 (C), 30.4 (CH_3), 22.1 (CH_3); HRMS (ESI+) m/z calcd for $C_{22}H_{27}O$ ($[M + H]^+$): 307.2056, found 307.2056; m/z calcd for $C_{22}H_{26}NaO$ ($[M + Na]^+$): 329.1876, found 329.1874.

*rac-(2S,5R)-2-(4-Methoxyphenyl)-7,7-dimethyl-4-methylene-5-phenyloxocane (**6b**).* The product was isolated as a yellow viscous oil (279 mg, 83% yield) using flash chromatography 20:1 hexane/EtOAc (R_f = 0.43, 10:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.31 (m, 7H), 6.97−6.94 (m, 2H), 5.29 (s, 1H), 5.11 (s, 1H), 4.60 (dd, J = 10.7 and 2.1 Hz, 1H), 3.90 (s, 3H), 3.92−3.84 (m, 2H), 3.61 (d, J = 11.9 Hz, 1H), 2.71−2.56 (m, 2H), 2.43 (d, J = 13.6 Hz, 1H), 1.53 (dd, J = 14.1 and 2.0 Hz, 1H), 1.18 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C), 151.3 (C), 145.9 (C), 136.1 (C), 128.4 (CH), 127.1 (CH), 126.1 (CH), 114.8 (CH_2), 113.8 (CH), 86.2 (CH), 77.5 (CH_2), 55.4 (CH_3), 48.5 (CH), 42.1 (CH_2), 39.5 (CH_2), 35.5 (C), 30.3 (CH_3), 22.1 (CH_3); HRMS (ESI+) m/z calcd for $C_{23}H_{29}O_2$ ($[M + H]^+$): 337.2162, found 337.2160.

*rac-(2S,5R)-7,7-Dimethyl-4-methylene-5-phenyl-2-p-tolyloxocane (**6c**).* The product was isolated as a yellow viscous oil (256 mg, 80% yield) using flash chromatography 25:1 hexane/EtOAc (R_f = 0.53, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 7.23−7.15 (m, 4H), 5.24 (s, 1H), 5.07 (s, 1H), 4.56 (d, J = 10.7 Hz, 1H), 3.89−3.75 (m, 2H), 3.55 (d, J = 11.9 Hz, 1H), 2.63 (dd, J = 14.0 and 13.5 Hz, 1H), 2.58−2.51 (m, 1H), 2.41−2.37 (m, 1H), 2.35 (s, 3H), 1.47 (d, J = 14.0 Hz, 1H), 1.12 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (C), 145.9 (C), 140.9 (C), 137.0 (C), 129.1 (CH), 128.4 (CH), 127.1 (CH), 126.2 (CH), 125.8 (CH), 114.8 (CH_2), 86.5 (CH), 77.5 (CH_2), 48.5 (CH), 42.2 (CH_2), 39.6 (CH_2), 35.6 (C), 30.4 (CH_3), 22.1 (CH_3), 21.3 (CH_3); HRMS (ESI+) m/z calcd for $C_{23}H_{29}O$ ($[M + H]^+$): 321.2213, found 321.2214; m/z calcd for $C_{23}H_{28}NaO$ ($[M + Na]^+$): 343.2032, found 343.2028.

*rac-(2S,5R)-2-(4-Chlorophenyl)-7,7-dimethyl-4-methylene-5-phenyloxocane (**6d**).* The product was isolated as a yellow viscous oil (275 mg, 81% yield) using flash chromatography 25:1 hexane/EtOAc (R_f = 0.55, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 8H), 7.20−7.14 (m, 1H), 5.25 (s, 1H), 5.06 (s, 1H), 4.55 (dd, J = 10.6 and 2.4 Hz, 1H), 3.86−3.77 (m, 2H), 3.54 (d, J = 11.8 Hz, 1H), 2.57 (dd, J = 14.0 and 13.3 Hz, 1H), 2.50−2.42 (m, 1H), 2.36 (dd, J = 13.5 and 2.4 Hz, 1H), 1.47 (dd, J = 14.0 and 1.9 Hz, 1H), 1.11 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0 (C), 145.7 (C), 142.3 (C), 133.0 (C), 128.5 (CH), 128.5 (CH), 127.3 (CH), 127.1 (CH), 126.3 (CH), 115.1 (CH_2), 85.8 (CH), 77.6 (CH_2), 48.4 (CH), 42.2 (CH_2), 39.5 (CH_2), 35.6 (C), 30.4 (CH_3), 22.1 (CH_3); HRMS (ESI+) m/z calcd for $C_{22}H_{26}ClO$ ($[M + H]^+$): 341.1667, found 341.1665; m/z calcd for $C_{22}H_{25}ClNaO$ ($[M + Na]^+$): 363.1486, found 363.1488.

*rac-(2S,5R)-7,7-Dimethyl-4-methylene-5-phenyl-2-vinyloxocane (**6e**).* The product was isolated as a yellow oil (179 mg, 70% yield) using flash chromatography 50:1 hexane/EtOAc (R_f = 0.56, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.17 (m, 5H), 5.93 (ddd, J = 17.3, 10.6, and 5.6 Hz, 1H), 5.30 (dt, J = 17.3 and 1.5 Hz, 1H), 5.18 (s, 1H), 5.12 (dt, J = 10.6 and 1.4, 1H), 4.96 (s, 1H), 4.07−3.99 (m, 1H), 3.75 (dd, J = 13.3 and 2.7 Hz, 1H), 3.70 (d, J = 11.9 Hz, 1H), 3.47 (dd, J = 11.9 and 0.9 Hz, 1H), 2.48 (dd, J = 13.9 and 13.3 Hz, 1H), 2.32−2.24 (m, 2H), 1.39 (dd, J = 13.9 and 1.9 Hz, 1H), 1.05 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (C), 145.9 (C), 139.8 (CH), 128.4 (CH), 127.1 (CH), 126.2 (CH), 114.7 (CH_2), 114.6 (CH_2), 85.0 (CH), 77.3 (CH_2), 48.5 (CH), 39.4 (CH_2), 39.2 (CH_2), 35.4 (C), 30.4 (CH_3), 22.1 (CH_3); HRMS (ESI+) m/z calcd for $C_{18}H_{24}NaO$ ($[M + Na]^+$): 279.1719, found 279.1737.

*rac-(2S,5R)-7,7-Dimethyl-4-methylene-5-phenyl-2-styryloxocane (**6f**).* The product was isolated as a yellow viscous oil (275 mg, 83% yield) using flash chromatography 25:1 hexane/EtOAc (R_f = 0.58, 15:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.29 (m, 10H), 6.67 (d, J = 16.0 Hz, 1H), 6.31 (dd, J = 16.0 and 5.8 Hz, 1H), 5.22 (s, 1H), 5.02 (s, 1H), 4.26−4.20 (m, 1H), 3.81−3.74 (m, 2H), 3.53 (d, J = 11.9 Hz, 1H), 2.54 (t, J = 13.5 Hz, 1H), 2.43−2.33 (m, 2H), 1.43 (d, J = 13.5 Hz, 1H), 1.10 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2 (C), 145.8 (C), 137.1 (C), 131.1 (CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 127.6 (CH), 127.1 (CH), 126.6 (CH), 126.2 (CH), 114.8 (CH_2), 84.8 (CH), 77.5 (CH_2), 48.5 (CH), 39.8 (CH_2), 39.2 (CH_2), 35.5 (C), 30.4 (CH_3), 22.1 (CH_3); HRMS (ESI+) m/z calcd for $C_{24}H_{29}O$ ($[M + H]^+$): 333.2213, found 333.2208; m/z calcd for $C_{24}H_{28}NaO$ ($[M + Na]^+$): 355.2032, found 355.2023.

*rac-(2S,5R)-7,7-Dimethyl-4-methylene-5-phenyl-2-((E)-prop-1-enyl)oxocane (**6g**).* The product was isolated as a yellow oil (221 mg, 82% yield) using flash chromatography 25:1 hexane/EtOAc (R_f = 0.56, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 5.75 (dq, J = 15.4 and 6.4 Hz, 1H), 5.59 (ddd, J = 15.4, 6.3, and 1.1 Hz, 1H), 5.17 (s, 1H), 4.95 (s, 1H), 4.02−3.96 (m, 1H), 3.72 (dd, J = 13.2 and 2.6 Hz, 1H), 3.69 (d, J = 12.0 Hz, 1H), 3.46 (d, J = 12.0 Hz, 1H), 2.49 (dd, J = 14.0 and 13.2 Hz, 1H), 2.33−2.20 (m, 2H), 1.72 (d, J = 6.4 Hz, 3H), 1.39 (dd, J = 14.0 and 2.1 Hz, 1H), 1.05 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (C), 145.9 (C), 132.8 (CH), 128.4 (CH), 127.1 (CH), 126.5 (CH), 126.1 (CH), 114.5 (CH_2), 85.1 (CH), 77.3 (CH_2), 48.5 (CH), 39.7 (CH_2), 39.2 (CH_2), 35.4 (C), 30.4 (CH_3), 22.1 (CH_3), 17.9 (CH_3); HRMS (ESI+) m/z calcd for $C_{19}H_{27}O$ ($[M + H]^+$): 271.2056, found 271.2051.

*rac-(2S,5R)-7,7-Dimethyl-4-methylene-2-((E)-pent-1-enyl)-5-phenyloxocane (**6h**).* The product was isolated as a yellow oil (223 mg, 75% yield) using flash chromatography 25:1 hexane/EtOAc (R_f = 0.49, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 5.77−5.68 (m, 1H), 5.56 (ddd, J = 15.5, 6.3, and 1.3 Hz, 1H), 5.17 (s, 1H), 4.96 (s, 1H), 4.04−3.97 (m, 1H), 3.74 (dd, J = 13.1 and 2.3 Hz, 1H), 3.68 (d, J = 12.0 Hz, 1H), 3.47 (d, J = 12.0 Hz, 1H), 2.49 (dd, J = 13.9 and 13.1 Hz, 1H), 2.34−2.19 (m, 2H), 2.07−2.01 (m, 2H), 1.46−1.37 (m, 3H), 1.05 (s, 3H), 0.95−0.89 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (C), 145.9 (C), 131.7 (CH), 131.5 (CH), 128.4 (CH), 127.2 (CH), 126.2 (CH), 114.5 (CH_2), 85.3 (CH), 77.3 (CH_2), 48.5 (CH), 40.0 (CH_2), 39.2 (CH_2), 35.4 (C), 34.6 (CH_2), 30.4 (CH_3), 22.4 (CH_2), 22.1 (CH_3), 13.9 (CH_3); HRMS (ESI+) m/z calcd for $C_{21}H_{31}O$ ($[M + H]^+$): 299.2369, found 299.2370; m/z calcd for $C_{21}H_{30}NaO$ ($[M + Na]^+$): 321.2189, found 321.2192.

*rac-(2S,5R)-7,7-Dimethyl-2-((E)-4-methyl-1-phenylpent-1-enyl)-4-methylene-5-phenyloxocane (**6i**).* The product was isolated as a yellow viscous oil (275 mg, 71% yield) using flash chromatography 30:1 hexane/EtOAc (R_f = 0.56, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.13 (m, 10H), 5.85 (t, J = 7.4 Hz, 1H), 5.08 (s, 1H), 4.80 (s, 1H), 4.19−4.15 (m, 1H), 3.73−3.66 (m, 2H), 3.49 (d, J = 11.9 Hz, 1H), 2.38 (t, J = 13.6 Hz, 1H), 2.21−2.15 (m, 2H), 1.86−1.83 (m, 2H), 1.69−1.61 (m, 1H), 1.33−1.30 (m, 1H), 1.06 (s, 3H), 0.89−0.84 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (C), 146.1 (C), 143.3 (C), 139.6 (C), 129.5 (CH), 128.4 (CH), 128.0 (CH), 127.3 (CH), 127.1 (CH), 126.7 (CH), 126.1 (CH), 114.3 (CH_2), 88.7 (CH), 77.3 (CH_2), 48.6 (CH), 39.5 (CH_2), 38.8 (CH_2), 37.7 (CH_2), 35.6 (C), 30.3 (CH_3), 29.0 (CH), 22.7 (CH_3), 22.7 (CH_3), 22.1 (CH_3); HRMS (ESI+) m/z calcd for $C_{28}H_{37}O$ ($[M + H]^+$): 389.2839, found 389.2842; m/z calcd for $C_{28}H_{36}NaO$ ($[M + Na]^+$): 411.2658, found 411.2668.

*5,5-Dimethyl-4,7-dimethylene-2-phenyloxocane (**8a**).* The product was isolated as a yellow viscous oil (126 mg, 52% yield) using flash chromatography 30:1 hexane/EtOAc (R_f = 0.51, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.26 (m, 5H), 5.07 (s, 1H), 4.96 (s, 1H), 4.81 (s, 1H), 4.79 (s, 1H), 4.54 (dd, J = 10.6 and 2.3 Hz, 1H), 4.36 (d, J = 14.7 Hz, 1H), 4.26 (d, J = 14.7 Hz, 1H), 3.10 (d, J = 13.5 Hz, 1H), 2.63 (ddd, J = 13.6, 10.6, and 2.0 Hz, 1H), 2.49 (dd, J = 13.6 and 2.3 Hz, 1H), 1.92 (d, J = 13.5 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (C), 147.5 (C), 143.6 (C), 128.5 (CH), 127.4 (CH), 126.0 (CH), 111.9 (CH_2), 111.3 (CH_2), 88.0 (CH), 74.0 (CH_2), 44.6 (CH_2), 42.5 (CH_2), 38.4 (C), 31.1 (CH_3), 25.8 (CH_3); HRMS (ESI+) m/z calcd for $C_{17}H_{23}O$ ($[M + H]^+$): 243.1743, found 243.1742; m/z calcd for $C_{17}H_{22}NaO$ ($[M + Na]^+$): 265.1563, found 265.1560.

*2-(4-Methoxyphenyl)-5,5-dimethyl-4,7-dimethyleneoxocane (**8b**).* The product was isolated as a yellow viscous oil (150 mg, 55% yield) using flash chromatography 10:1 hexane/EtOAc (R_f = 0.35, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 8.6 and 0.5 Hz, 2H), 6.89 (dd, J = 8.6 and 1.0 Hz, 2H), 5.06 (s, 1H), 4.94 (s, 1H), 4.80 (s, 1H), 4.78 (s, 1H), 4.50 (d, J = 10.5 Hz, 1H), 4.34 (d, J = 14.6 Hz, 1H), 4.25 (d, J = 14.6 Hz, 1H), 3.81 (s, 3H), 3.08 (d, J = 13.5 Hz, 1H), 2.63 (dd, J = 13.7 and 10.5 Hz, 1H), 2.47 (d, J = 13.7 Hz,

DOI: 10.1021/acs.joc.5b02260
J. Org. Chem. 2016, 81, 2704−2712

1H), 1.92 (d, J = 13.5 Hz, 1H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 156.1 (C), 147.5 (C), 135.9 (C), 127.2 (CH), 113.8 (CH), 111.8 (CH_2), 111.2 (CH_2), 87.6 (CH), 73.9 (CH_2), 55.5 (CH_3), 44.6 (CH_2), 42.3 (CH_2), 38.4 (C), 31.1 (CH_3), 25.8 (CH_3); HRMS (ESI+) m/z calcd for $C_{18}H_{25}O_2$ ($[M + H]^+$): 273.1849, found 273.1847; m/z calcd for $C_{18}H_{24}NaO_2$ ($[M + Na]^+$): 295.1669, found 295.1666.

*5,5-Dimethyl-4,7-dimethylene-2-(E)-styryloxocane (**8c**).* The product was isolated as a yellow viscous oil (137 mg, 51% yield) using flash chromatography 30:1 hexane/EtOAc (R_f = 0.52, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.21 (m, 5H), 6.65 (d, J = 16.0 Hz, 1H), 6.30 (ddd, J = 16.0, 5.6, and 1.6 Hz, 1H), 5.04 (s, 1H), 4.92 (s, 1H), 4.81 (s, 1H), 4.77 (s, 1H), 4.34 (d, J = 14.6 Hz, 1H), 4.22−4.15 (m, 2H), 2.95 (d, J = 13.5 Hz, 1H), 2.52−2.43 (m, 2H), 1.90 (d, J = 13.5 Hz, 1H), 1.13 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (C), 147.4 (C), 137.1 (C), 131.0 (CH), 129.8 (CH), 128.7 (CH), 127.6 (CH), 126.6 (CH), 112.0 (CH_2), 111.2 (CH_2), 85.7 (CH), 73.5 (CH_2), 44.6 (CH_2), 40.3 (CH_2), 38.5 (C), 31.0 (CH_3), 26.0 (CH_3); HRMS (ESI+) m/z calcd for $C_{19}H_{25}O$ ($[M + H]^+$): 269.1900, found 269.1893; m/z calcd for $C_{19}H_{24}NaO$ ($[M + Na]^+$): 291.1719, found 291.1710.

*5,5-Dimethyl-4,7-dimethylene-2-((E)-prop-1-enyl)oxocane (**8d**).* The product was isolated as a yellow oil (121 mg, 59% yield) using flash chromatography 30:1 hexane/EtOAc (R_f = 0.57, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (ddd, J = 15.4, 6.4, and 1.1 Hz, 1H), 5.58 (ddd, J = 15.4, 6.1, and 1.5 Hz, 1H), 4.99 (s, 1H), 4.85 (s, 1H), 4.76 (s, 1H), 4.73 (s, 1H), 4.26 (d, J = 14.6 Hz, 1H), 4.11 (d, J = 14.6 Hz, 1H), 3.98−3.91 (m, 1H), 2.91 (d, J = 13.5 Hz, 1H), 2.41−2.29 (m, 2H), 1.85 (d, J = 13.5 Hz, 1H), 1.71 (d, J = 6.4 Hz, 3H), 1.10 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (C), 147.5 (C), 132.7 (CH), 126.4 (CH), 111.8 (CH_2), 110.9 (CH_2), 85.9 (CH), 73.3 (CH_2), 44.5 (CH_2), 40.2 (CH_2), 38.4 (C), 31.0 (CH_3), 25.9 (CH_3), 18.0 (CH_3). HRMS (ESI+) m/z calcd for $C_{14}H_{23}O$ ($[M + H]^+$): 207.1743, found 207.1742; m/z calcd for $C_{14}H_{22}NaO$ ($[M + Na]^+$): 229.1563, found 229.1545.

*5,5-Dimethyl-4,7-dimethylene-2-((E)-pent-1-enyl)oxocane (**8e**).* The product was isolated as a yellow oil (133 mg, 57% yield) using flash chromatography 30:1 hexane/EtOAc (R_f = 0.58, 20:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75−5.67 (m, 1H), 5.59−5.52 (m, 1H), 4.99 (s, 1H), 4.86 (s, 1H), 4.77 (s, 1H), 4.73 (s, 1H), 4.26 (d, J = 14.6 Hz, 1H), 4.12 (d, J = 14.6 Hz, 1H), 4.00−3.93 (m, 1H), 2.91 (d, J = 13.5 Hz, 1H), 2.42−2.30 (m, 2H), 2.05−1.99 (m, 2H), 1.86 (d, J = 13.5 Hz, 1H), 1.44−1.40 (m, 2H), 1.10 (s, 3H), 1.06 (s, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (C), 147.6 (C), 131.5 (CH), 131.5 (CH), 111.8 (CH_2), 110.9 (CH_2), 86.0 (CH), 73.3 (CH_2), 44.5 (CH_2), 40.4 (CH_2), 38.4 (C), 34.6 (CH_2), 31.0 (CH_3), 25.9 (CH_3), 22.4 (CH_2), 13.9 (CH_3); HRMS (ESI+) m/z calcd for $C_{16}H_{27}O$ ($[M + H]^+$): 235.2056, found 235.2053; m/z calcd for $C_{16}H_{26}NaO$ ($[M + Na]^+$): 257.1876, found 257.1872.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02260.

Stereochemical assignments as well as copies of ^{1}H, ^{13}C, and NOE NMR spectra for new compounds. (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: barbero@qo.uva.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Ministry of Science and Technology of Spain (CTQ2009-09302) and the "Junta de Castilla y León" (GR170) for financial support.

■ REFERENCES

(1) The term "trishomoallylic alcohol" has been previously used to name this type of alcohols, see within others: (a) Blaisdell, T. P.; Caya, T. C.; Zhang, L.; Sanz-Marco, A.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 9264−9267. (b) Mcdonald, F. E.; Singhi, A. D. *Tetrahedron Lett.* **1997**, *38*, 7683−7686. (c) Hilton, M. J.; Cheng, B.; Buckley, B. R.; Xu, L.; Wiest, O.; Sigman, M. S. *Tetrahedron* **2015**, *71*, 6513−6518. (d) McCombs, J. R.; Michel, B. W.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 3609−3613. (e) Morimoto, Y. *Org. Biomol. Chem.* **2008**, *6*, 1709−1719. (f) D, M.; Salik, S.; Fox, D. J. *J. Org. Chem.* **2010**, *75*, 2157−2168. (g) Takano, S.; Sugihara, Y.; Ogasawara, K. *Synlett* **1992**, *1992*, 668−670. (h) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707−11711.

(2) (a) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413−445. (b) Pastor, I.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925−957. (c) Pastor, I.; Yus, M. *Curr. Org. Chem.* **2012**, *16*, 1277−1312. (d) Han, X.; Peh, G.; Floreancig, P. E. *Eur. J. Org. Chem.* **2013**, *2013*, 1193−1208.

(3) Ghosh, A. K.; Shin, D.; Schiltz, G. *Heterocycles* **2002**, *58*, 659−666.

(4) Damera, K.; Yu, B.; Wang, B. *J. Org. Chem.* **2015**, *80*, 5457−5463.

(5) (a) Reddy, B. V. S.; Borkar, P.; Chakravarthy, P. P.; Yadav, J. S.; Gree, R. *Tetrahedron Lett.* **2010**, *51*, 3412−3416. (b) Elsworth, J. D.; Willis, C. L. *Chem. Commun.* **2008**, 1587−1589.

(6) Reddy, B. V. S.; Kumar, H.; Reddy, P. S.; Singarapu, K. K. *Eur. J. Org. Chem.* **2014**, *2014*, 4234−4238.

(7) (a) Barbero, A.; Pulido, F. J. *Chem. Soc. Rev.* **2005**, *34*, 913−920. (b) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Rubio, R.; Fleming, I. *Tetrahedron Lett.* **1992**, *33*, 5841−5842.

(8) (a) Barbero, A.; Castreño, P.; Pulido, F. J. *J. Am. Chem. Soc.* **2005**, *127*, 8022−8023. (b) Barbero, A.; Blanco, A.; Pulido, F. J. *J. Org. Chem.* **2005**, *70*, 6876−6883. (c) Barbero, A.; Blanco, Y.; Pulido, F. J. *Chem. Commun.* **2001**, 1606−1607. (d) Pulido, F. J.; Barbero, A.; Castreño, P. *J. Org. Chem.* **2011**, *76*, 5850−5855.

(9) (a) Pulido, F. J.; Barbero, A.; Blanco, Y. *Org. Biomol. Chem.* **2011**, *9*, 1454−1458. (b) Pulido, F. J.; Barbero, A.; Val, P.; Diez, A.; González-Ortega, A. *Eur. J. Org. Chem.* **2012**, *2012*, 5350−5356.

(10) (a) Barbero, A.; Diez-Varga, A.; Pulido, F. J. *Org. Lett.* **2013**, *15*, 5234−5237. (b) Diez-Varga, A.; Barbero, H.; Pulido, F. J.; González-Ortega, A.; Barbero, A. *Chem. - Eur. J.* **2014**, *20*, 14112−14119.

(11) Wu, W.-B.; Zhang, H.; Liu, H.-C.; Dong, S.-H.; Wu, Y.; Ding, J. *Tetrahedron* **2014**, *70*, 3570−3575.

(12) Fang, X.; DI, Y.-T.; He, H.-P.; Liu, H.-Y.; Zhang, Z.; Ren, Y.-L.; Gao, Z.-L.; Gao, S.; Hao, X.-J. *Org. Lett.* **2008**, *10*, 1905−1908.

(13) Nagakura, Y.; Nugroho, A. E.; Hirasawa, Y.; Hosoya, T.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Morita, H. *J. Nat. Med.* **2013**, *67*, 381−385.

(14) Barbero, A.; Pulido, F. J. *Synthesis* **2004**, *2004*, 779−785.

(15) Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* **2001**, *2001*, 4445−4450.

(16) Although compounds **1** couldn't be isolated as pure compounds, their identity could be confirm by HRMS. **1a**: HRMS (ESI+) m/z calcd for $C_{17}H_{29}OSi$ ($[M+H]^+$) 277.1982, found 277.1985. **1b**: HRMS (ESI+) m/z calcd for $C_{19}H_{32}NaOSi$ ($[M+Na]^+$) 327.2117, found 327.2115.

(17) The reaction of the corresponding bishomoallylic alcohols with aliphatic aldehydes was shown to be low yielding (ref 10b).

(18) We think that **4b** would be obtained by cyclization of **5**, byproduct of the synthesis of alcohol **1a**. Since **1a** is always prepared in situ and readily cyclized, this would explain the occasional obtention of **4b**.

(19) Bissing, D. E.; Speziale, A. J. *J. Am. Chem. Soc.* **1965**, *87*, 2683−2690.

DOI: 10.1021/acs.joc.5b02260
J. Org. Chem. 2016, 81, 2704−2712

(20) (a) Blumenkopf, T. A.; Bratz, M.; Castafieda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386−4398. (b) Biumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399−4403.
(21) The low polarity of oxocanes with R = Ph, MePh or ClPh made difficult their purification and isolation.
(22) (a) Lian, Y.; Hinkle, R. J. *J. Org. Chem.* **2006**, *71*, 7071−7074. (b) Dobbs, A. P.; Martinović, S. *Tetrahedron Lett.* **2002**, *43*, 7055−7057.
(23) Within others, see: (a) Jiménez-González, L.; García-Muñoz, S.; Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. - Eur. J.* **2007**, *13*, 557−568. (b) Wu, J.; Pu, Y.; Panek, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 18440−18446.
(24) Bottoni, A.; Costa, A. L.; Tommaso, D. D.; Rossi, I.; Tagliavini, E. *J. Am. Chem. Soc.* **1997**, *119*, 12131−12135.
(25) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006−5017.
(26) Lewinski, J.; Horeglad, P.; Tratkiewicz, E.; Justyniak, I.; Ochal, Z. *J. Organomet. Chem.* **2005**, *690*, 3697−3699.
(27) The acid catalyzed isomerization of epoxides to allylic alcohols has been previously reported. For examples, see: (a) Chapman, H. A.; Herbal, K.; Motherwell, W. B. *Synlett* **2010**, *2010*, 595−598. (b) Orru, R. V. A.; Mayer, S. F.; Kroutil, W.; Faber, K. *Tetrahedron* **1998**, *54*, 859−874.
(28) (a) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193−4205. (b) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, *6*, 1091−1099.
(29) Falshaw, C. P.; King, T. J.; Imre, S.; Islimyeli, S.; Thomson, R. H. *Tetrahedron Lett.* **1980**, *21*, 4951.
(30) Kinnel, R. B.; Dieter, R. K.; Meinwald, J.; Van Eugen, D.; Clardy, J.; Eisner, T.; Stallard, M. O.; Fenical, W. *Proc. Natl. Acad. Sci. U. S. A.* **1979**, *76*, 3576.

DOI: 10.1021/acs.joc.5b02260
J. Org. Chem. 2016, 81, 2704−2712