ORGANIC LETTERS

2012
Vol. 14, No. 23
5904–5907

Iron(III) Catalyzed Direct Synthesis of *cis*-2,7-Disubstituted Oxepanes. The Shortest Total Synthesis of (+)-Isolaurepan

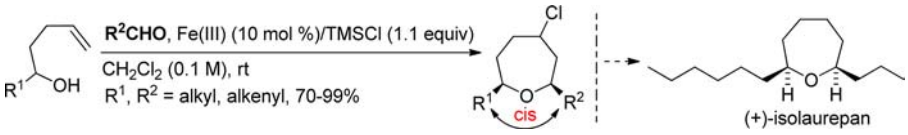
Martín A. Purino,[†] Miguel A. Ramírez,[†] Antonio H. Daranas,[†] Víctor S. Martín,[†] and Juan I. Padrón*[,†,‡]

Instituto Universitario de Bio-Orgánica "Antonio González", Departamento de Química Orgánica, Universidad de La Laguna, C/Astrofísico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Spain, and Instituto de Productos Naturales y Agrobiología, CSIC, C/Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain

jipadron@ipna.csic.es

Received October 15, 2012

ABSTRACT



Prins cyclization of *bis*-homoallylic alcohols with aldehydes catalyzed by iron(III) salts shows excellent *cis* selectivity and yields to form 2,7-disubstituted oxepanes. The iron(III) is able to catalyze this process with unactivated olefins. This cyclization was used as the key step in the shortest total synthesis of (+)-isolaurepan.

Seven-membered oxacycles (oxepanes) are a common structural unit present and widespread in many bioactive marine natural products.[1] The common structural features are the 2,7-disubstituted oxepanes, with different halide atoms at the side chains in the case of the simpler Laurencia acetogenin metabolites (Figure 1),[2] or being part of highly complex natural compounds such as the marine polycyclic toxins.[3]

The development of new methodologies to gain access to this type of oxacycle has steadily increased in recent years mainly focusing on two major strategies of cyclization: through C−C and C−O bond formation.[4] However simple, direct construction of oxepanes is not an easy task. Ideally, such methodology should use accessible starting

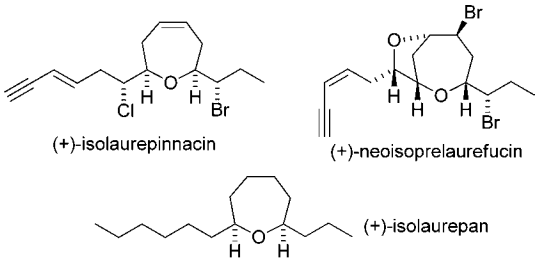


Figure 1. Some representative lauroxepanes and (+)-isolaurepan, the fully saturated core of (+)-isolaurepinnacin.

[†] IUBO, Universidad de La Laguna.
[‡] IPNA, CSIC.

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(2) (a) Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, 4135–4138. (b) Suzuki, M.; Kurata, K.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2953–2955. (c) Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081–4084.

(3) (a) Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, 4135–4138. (b) Suzuki, M.; Kurata, K.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2953–2955. (c) Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081–4084.

(4) (a) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136–4137. (b) Álvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953–1980. (c) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631–12670. (d) Marmsäter, F. P.; West, F. G. *Chem.—Eur. J.* **2002**, *8*, 4347–4353. (d) Batchelor, R.; Harvey, J. E.; Northcote, P. T.; Teesdale-Spittle, P.; Hoberg, J. O. *J. Org. Chem.* **2009**, *74*, 7627–7632. (e) Furuta, H.; Hasegawa, Y.; Mori, Y. *Org. Lett.* **2009**, *11*, 4382–4385. (f) Ortega, N.; Martín, V. S.; Martín, T. *J. Org. Chem.* **2010**, *75*, 6660–6672. (g) Kleinke, A. S.; Webb, D.; Jamison, T. F. *Tetrahedron* **2012**, *68*, 6999–7018.

10.1021/ol3028016
Published on Web 11/20/2012

materials, achieving stereochemical control (usually *cis*) of the (α,α′)-substituents adjacent to the oxygen atoms.

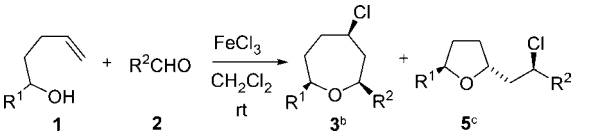
With our research group's experience in the synthesis of oxacycles of various sizes,[4f] we now focused on developing a simple and direct methodology to gain access to medium-size-ring oxacycles in a sustainable metal catalysis context,[5] using nontoxic, abundant, and biologically relevant iron(III).[6] We decided to use Prins cyclization,[7] in the direct synthesis of oxepanes considering the few precedents found in the literature.[8] The seminal work of Overman et al. was based on the indirect cyclization of mixed acetals derived from silyl activated 4-alken-1-ols and promoted by an excess of Lewis acid.[9] Herein we report studies of Prins cyclization, with unactivated olefins, in the direct synthesis of oxepanes and its utility in the total synthesis of (+)-isolaurepan.

Prins cyclization of 4-alken-1-ol (**1**, R^1 = H) and isovaleraldehyde was initially performed in dry CH_2Cl_2 using stoichiometric amounts of $FeCl_3$. The desired all *cis*-disubstituted oxepane **3a** was obtained in 56% yield contaminated with 41% of the monosubstituted tetrahydrofuran (THF) **5a** (Table 1, entry 1). The oxepanes **3b** and **3c** were obtained exclusively, without the presence of the corresponding THFs, using more hindered aldehydes (Table 1, entries 2 and 3).

Next, we tested this cyclization using secondary *bis*-homoallylic alcohols (**1**, $R^1 \neq$ H) under the same reaction conditions (Table 1). The all *cis*-2,4,7-trisubstituted oxepanes were obtained as the major compounds (Table 1, entries 6−10, **3f**−**3j**). Again, with a hindered aldehyde as pivalaldehyde, the oxepane **3g** was formed exclusively in good yield (Table 1, entry 7). At this point, we had very good overall yields from the cyclization process but with high yields of THF derivatives (Table 1, **5b**−**5g**). Therefore, we applied our previously described catalytic system formed from iron(III) salts and trimethylsilyl chloride in the synthesis of oxepanes (Table 2).[6c]

To our delight, the application of such a catalytic system to the Prins cyclization led, with very good yields, to the mixtures of oxepanes (**3** and **4**) without the presence of THF derivatives **5** (Table 2). With *bis*-homoallylic alcohols **1**, the iron sources $FeCl_3$ and $Fe(acac)_3$ catalyzed the cyclization, affording, in both cases, a mixture of *cis*-2,7-dialkyl-oxepanes differing in the stereochemistry of the

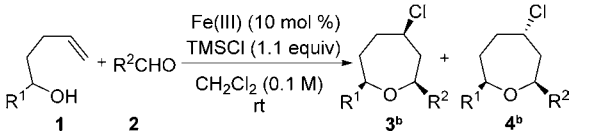
Table 1. Prins Cyclization of Oxepanes Using Stoichiometric Amounts of Iron(III) Chloride[a]



entry	R^1	R^2		yield[d] (**3**)(%)	yield[d] (**5**)(%)
1	H	*i*-Bu	**3a**, **5a**	56	41
2	H	*c*-C_6H_{11}	**3b**	60	0
3	H	*t*-Bu	**3c**	70	0
4	H	*n*-C_6H_{13}	**3d**, **5b**	32	37
5	H	CH_2=$CH(CH_2)_2$	**3e**, **5c**	15	21
6	*n*-C_6H_{13}	*i*-Bu	**3f**, **5d**	42	33
7	*n*-C_6H_{13}	*t*-Bu	**3g**	75	0
8	*n*-C_6H_{13}	CH_2=$CH(CH_2)_2$	**3h**, **5e**	43	37
9	CH_2Ph	*i*-Bu	**3i**, **5f**	63	35
10	CH_2Ph	CH_2=$CH(CH_2)_2$	**3j**, **5g**	45	42[e]

[a] Reaction conditions: **1** (1.0 mmol), R^2CHO (1.1 mmol), and $FeCl_3$ (1.0 equiv) in dry CH_2Cl_2 (10 mL) at rt in an open atmosphere for 15 h. [b] The *cis* stereochemistry of the oxepanes was assigned by NOE experiments. [c] The relative stereochemistry of the THFs was determined by NMR studies on **5g** (see the Supporting Information (SI)). [d] Yields of products after purification by silica gel column chromatography. [e] Reaction time was 3 h; otherwise the final products are decomposed

Table 2. Iron(III)/TMSCl System Catalyzes the Direct Synthesis of Substituted Oxepanes[a]



entry	R^1	R^2		$FeCl_3$ yield[c] (%)	$Fe(acac)_3$ yield[c] (%)	ratio[d] (**3**:**4**) (%)
1	H	*i*-Bu	**3a**,**4a**	99	85	55:45
2	H	*c*-C_6H_{11}	**3b**,**4b**	99	92	73:27
3	H	*t*-Bu	**3c**,**4c**	75	60	72:28
4	H	*n*-C_6H_{13}	**3d**,**4d**	80	80	58:42
5	H	CH_2=$CH(CH_2)_2$	**3e**,**4e**	40	70	59:41
6	*n*-C_6H_{13}	*i*-Bu	**3f**, **4f**	90	85	60:40
7	*n*-C_6H_{13}	*t*-Bu	**3g**,**4g**	–	90	67:33
8	*n*-C_6H_{13}	*t*-Bu	**3g**,**4g**	90	–	71:29
9	*n*-C_6H_{13}	CH_2=$CH(CH_2)_2$	**3h**,**4h**	90	85	58:42
10	CH_2Ph	*i*-Bu	**3i**,**4i**	95	95	56:44
11	CH_2Ph	CH_2=$CH(CH_2)_2$	**3j**,**4j**	95	97	60:40

[a] Reaction conditions: **1** (1.0 mmol), R^2CHO (1.1 mmol), and $FeCl_3$ (0.1 mmol)/TMSCl (1.1 mmol) in dry CH_2Cl_2 (10 mL) at rt in an open atmosphere for 15 h. [b] The relative stereochemistry of the oxepanes was assigned by NOE experiments (see the SI). [c] Yields of products after purification by silica gel column chromatography. [d] The ratios were determined by ^{1}H NMR spectroscopy.

(5) Plietker, B. *Synlett* **2010**, *14*, 2049–2058.

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(7) (a) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413–445. (b) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925–957. (c) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2012**, *16*, 1277–1312.

(8) (a) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913–915. (b) Lolkema, L. D. M.; Hiemstra, H.; Mooiweer, H. H.; Speckamp, W. N. *Tetrahedron Lett.* **1988**, *29*, 6365–6368. (c) Furman, B.; Dziedzic, M.; Justyniak, I. *Tetrahedron* **2008**, *64*, 3103–3110.

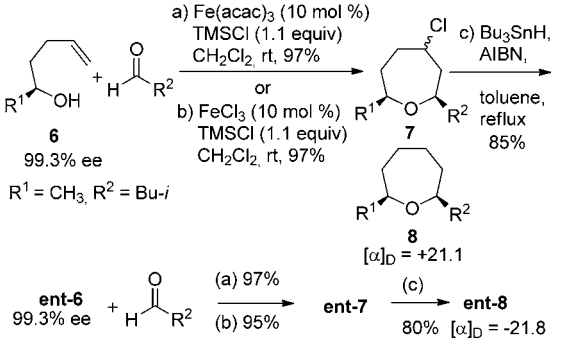
(9) (a) Overman, L. E.; Castañeda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303–1304. (b) Castañeda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695–5707. (c) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446–2452.

Cl-atom at C-4. Prins cyclization of 4-alkenol and isovaleraldehyde led to a 55:45 mixture of substituted oxepanes (**3a**/**4a**) with excellent yield (Table 2, entry 1). The yields are very good with both iron(III) sources, being slightly higher with $FeCl_3$. However, $Fe(acac)_3$ shows better results with aldehydes bearing functionalized groups as double bonds when $R^1 = H$ (Table 2, entry 5). It should be emphasized that the excellent yields obtained with functionalized aldehydes with both iron(III) sources (Table 2, entries 9 and 11) led the way to other functional groups. Prins cyclization led to 60:40 mixtures of oxepanes **3**/**4** except when a bulky aldehyde was used (Table 2, entries 2, 3, 7, and 8).[10]

It must be noted that, from a synthetic point of view, the absence of stereochemical control at the Cl-substituted carbon is not a limitation for the effective synthesis of the oxepane ring. The Cl-atom can be easily removed, yielding a single *cis*-2,7-disubstituted oxepane. To test the stereochemical behavior of the process and advance further synthetic applications, we decided to explore this cyclization using enantiomerically enriched secondary *bis*-homoallylic alcohols (Scheme 1).

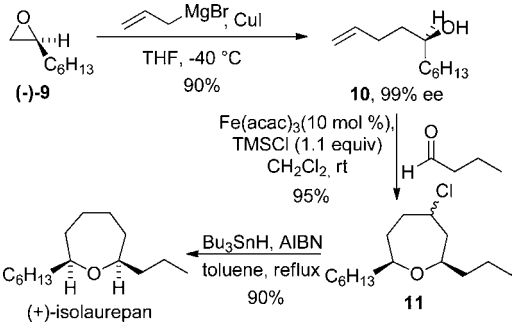
Prins cyclization with the commercially available (*S*)-hex-5-en-2-ol (**6**) and isovaleraldehyde led to oxepanes **7** in excellent yield using both iron(III) sources, $FeCl_3$ and $Fe(acac)_3$. The oxepane **8** was obtained in 85% yield after a subsequent dehalogenation reaction using *n*-Bu_3SnH and AIBN. We observed parallel results starting from the corresponding enantiomer of the *bis*-homoallylic alcohol **6** (Scheme 1). The overall yield to generate enantiomerically enriched *cis*-2,7-disubstituted oxepanes was in the 76−83% range.

Scheme 1. Synthesis of Enantiomerically Enriched *cis*-2,7-Disubstituted Oxepanes



With all these data in hand, we concentrated our efforts toward the total synthesis of (+)-isolaurepan using the described Prins cyclization as the key reaction step (Scheme 2). We planned this synthesis from the enantiomerically enriched *bis*-homoallylic alcohol **10** incorporating the *n*-hexyl group which was obtained in one step. Regioselective ring opening of the known epoxide (−)-**9**[11] with allyl magnesium bromide in the presence of CuI afforded the desired **10** in 90% yield (> 99 ee).[12]

Scheme 2. Total Synthesis of (+)-Isolaurepan through the Prins Cyclization



Prins cyclization of **10** with butyraldehyde was performed under standard reaction conditions, using $Fe(acac)_3$ as the iron(III) source,[13] to generate the desired oxepane **11** in 95% yield.[14] A final dehalogenation step led to formation of (+)-isolaurepan ($[\alpha]_D^{25} = +1.5$ (*c* 0.97, $CHCl_3$)) in 90% yield. From the enantiomerically enriched epoxide **9**, we have accomplished the shortest and most efficient total synthesis of (+)-isolaurepan with a 77% overall yield.[15] Furthermore with this total synthesis, we have shown that the cyclization proceeds without a loss in enantiopurity.

To gain insight into the reaction mechanism, mechanistic oriented experiments were performed. We propose that the reaction of the secondary *bis*-homoallylic alcohol **1**

(10) When this cyclization was performed using $Fe(acac)_3$ and isovaleraldehyde, in the presence of air and moisture, the target product was obtained in a remarkable 85% yield (scaled up to 3 g).

(11) (a) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130–4131. (b) Berkessel, A.; Rollmann, C.; Chamouleau, F.; Labs, S.; May, O.; Gröger, H. *Adv. Synth. Catal.* **2007**, *349*, 2697–2704.

(12) The epoxide (−)-**9** was prepared via hydrolytic kinetic resolution: (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gouul, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315. (b) Nielsen, L. P. C.; Stevenson, C. P.; Backmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362.

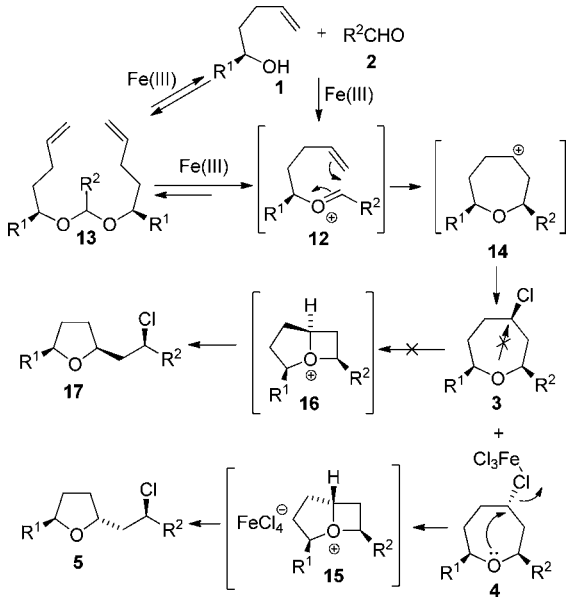
(13) The Prins cyclization with the racemic alcohol **10** and $FeCl_3$ as the catalyst led to the desired oxepane **11** as a *cis*/*trans* 60:40 mixture in 90% yield. However, this cyclization was improved using $Fe(acac)_3$ as the catalyst, and it was applied in the total synthesis of the (+)-isolaurepan in Scheme 2.

(14) The oxepane **11** was obtained as a *cis*/*trans* 60:40 mixture, with respect to the atom of chlorine. These isomers were isolated and characterized. See the SI.

(15) Synthesis of isolaurepan; (+)-isolaurepan: (a) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153–5161 (36% overall yield, $[\alpha]_D^{24} = +1.5$ (*c* 0.97, $CHCl_3$)). (b) Tripathi, D.; Kumar, P. *Tetrahedron Lett.* **2008**, *49*, 7012–7014 (30% overall yield, $[\alpha]_D^{25} = +1.5$ (*c* 0.97, $CHCl_3$)). (c) Pazos, G.; Pérez, M.; Gándara, Z.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2009**, *50*, 5285–5287 (11.5% overall yield, $[\alpha]_D^{20} = +1.7$ (*c* 0.94, $CHCl_3$)). (d) Tripathi, D.; Kumar, S.; Kumar, P. *Tetrahedron* **2009**, *65*, 2226–2231 (34% overall yield, $[\alpha]_D^{24} = +1.5$ (*c* 0.97, $CHCl_3$)). Formal synthesis: (e) Carreño, M. C.; Mazery, R. D.; Urbano, A.; Colobert, F.; Solladie, G. *Org. Lett.* **2004**, *6*, 297–299 (31% overall yield at intermediate of Kotsuki). (−)-Isolaurepan: (f) Prasad, K.; Anbarasan, P. *Tetrahedron: Asymmetry* **2007**, *18*, 1419–1427 (60% overall yield at intermediate of Kotsuki). Racemic synthesis: (g) Davies, M. J.; Moody, C. J. *Synlett* **1990**, 95–96 (58% overall yield). (h) Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83–94 (< 1%). (i) Ebine, M.; Suga, Y.; Sasaki, M. *Org. Biomol. Chem.* **2010**, *8*, 39–42 (29% overall yield).

and an aldehyde **2** catalyzed by ferric chloride generates the oxocarbenium ion **12**, which can also be generated from the acetal **13** which was isolated and characterized.[16] The intermediate **12** evolves to the corresponding oxepanes **3** and **4** via the carbocation **14**, explaining the ratio between the oxepanes **3** and **4**. THFs **5** and **17** could be generated from the corresponding bicycles **15** and **16** (Scheme 3).

Scheme 3. Mechanistic Proposal in the Synthesis of 2,7-Disubtituted Oxepanes Catalyzed by Iron(III)



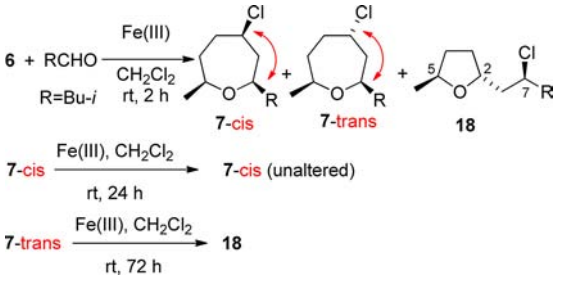
However, we have only observed oxepanes **3** and **4** and THF **5** as products of this reaction and suspected that oxepane **4** was being transformed into the THF **5** (Tables 1 and 2).

Next, to confirm that the trisubstituted oxepane **4** is transformed into THF **5**, we decided to run a Prins cyclization using the commercially available *bis*-homoallylic alcohol **6** enantiomerically enriched. We used 1.0 equiv of iron(III) chloride to obtain the THF ring in addition to the oxepane rings (Scheme 4). All the products were isolated and fully characterized.[16]

The oxepane **7**-*cis* was stable upon treatment with catalytic amounts of iron(III) chloride during 24 h at rt (Scheme 4). However, treatment of the oxepane **7**-*trans* under the conditions mentioned above afforded a mixture of the THF **18** with the starting oxepane **7**-*trans* (Scheme 4). Longer reaction times led exclusively to the THF **18** as the final product.[17]

All these experimental results show the bicycle **15** as an intermediate to the THF **5** and support the mechanistic

Scheme 4. Experiments Performed to Contrast the Mechanistic Proposal



proposal of Scheme 3.[18] In the oxepane **4**, the oxygen of the ether participates in a transannular cyclization through an S_N2 due to the optimal spatial requirement with the Cl-atom (internal angle O−C−Cl, 166.7°), leading to **15**. The leaving group nature of the Cl-ion is enhanced by coordination with $FeCl_3$. The attack of the chloride to the carbon adjacent to the oxonium, with R^2 as the substituent, led to the thermodynamically more stable THF **5**. In the case of bulky substituents at this position (R^2 = *c*-C_6H_{11} and *t*-Bu) this attack is unfavorable, with the presence of THF **5** undetected (Table 1, entries 2, 3 and 7). However, in the oxepane **3**, the transannular cyclization is unfavorable because the oxygen and chlorine (internal angle O−C−Cl, 141.7°) did not meet the spatial requirement to form the bicycle **16** and therefore the tetrahydrofuran **17**.

In summary, we successfully developed an efficient Prins cyclization of *bis*-homoallylic alcohols with aldehydes catalyzed by iron(III) salts. The reaction provides a direct entry to *cis*-2,7-disubstituted oxepanes with excellent yields. Using this approach as a key step, we performed the shortest and most efficient total synthesis of (+)-isolaurepan, thus demonstrating the value of this methodology which uses unactivated olefins. The suitable experiments allowed us to propose a rational mechanism in the synthesis of 2,7-disubstituted oxepanes.

We have developed a general and useful route to the synthesis of a wide variety of functionalized *cis*-2,7-disubstituted oxepanes. Further application of this methodology to the total synthesis of natural products (more complex oxepanes) and computational studies are underway.

Acknowledgment. This research was supported by the Spanish MINECO, cofinanced by the European Regional Development Fund (ERDF) (CTQ2011-28417-C02-01/BQU).

Supporting Information Available. ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) For more details, see the SI.

(17) The relative stereochemistry of the tetrahydrofuran **18** was determined by NMR studies. See the SI.

(18) Our mechanistic proposal completes the Overman studies in the synthesis of 2,7-disubstituted oxepanes from mixed acetals derived from 4-penten-1-ol (see ref 8b).