Organic LETTERS

Letter

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Approach to Merosesquiterpenes via Lewis Acid Catalyzed Nazarov-Type Cyclization: Total Synthesis of Akaol A

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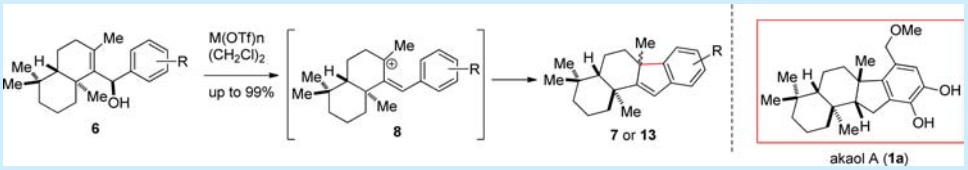
Supporting Information



ABSTRACT: A Lewis acid catalyzed Nazarov-type cyclization of arylvinylcarbinol has been developed for the asymmetric synthesis of carbotetracyclic core of merosesquiterpenes. The reaction works only in the presence of 2 mol % of $Sn(OTf)_2$ and $Bi(OTf)_3$ in dichloroethane under elevated temperature. The methodology offers the synthesis of a variety of enantioenriched arylvinylcarbinols from commercially available (3a*R*)-sclareolide **9** in six steps with an eventual concise total synthesis of marine sesquiterpene quinol, akaol A (**1a**).

Merosesquiterpenes are natural products of mixed biosynthetic origin (arising from polyketide-terpenoid) containing a sesquiterpene unit joined to a phenolic (or sometimes as quinone moiety).[1] Compounds bearing a bicyclic terpene (especially drimane) moiety are the most important group of this family, owing to their wide variety of structural types and potent biological activities.[2] Among various merosesquiterpenes,[3] pelorol (**1c**) (Figure 1) was isolated

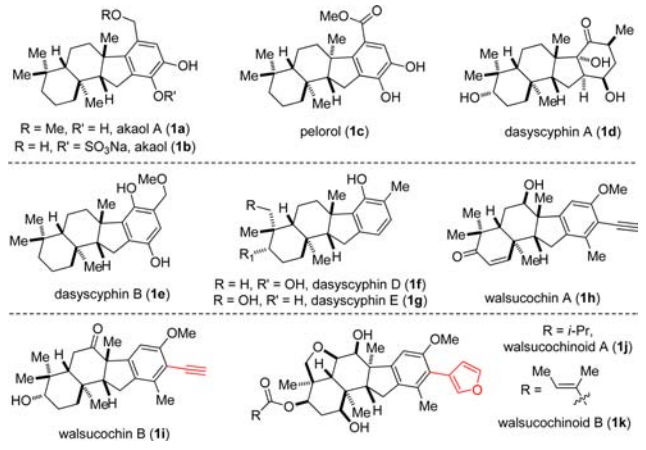


Figure 1. Selected merosesquinoids **1a**–**k**.

from *Dactylospongia elegans* in 2000[4] and akaol A (**1a**) was isolated from a Micronesian sponge of the genus *Aka* in 2003.[5] Other merosesquiterpenes, such as dasyscyphins A, B and D, E (**1d,e** and **1f,g**) were isolated from the ascomycete *Dasyscyphus niveus*.[6,7] In 2008, Yue and co-workers also isolated two unprecedented skeletons with C-24 nortriterpenoid structural motifs, walsucochins A (**1h**) and B (**1i**), from *Walsura cochinchinensis*.[8] These novel C-24 nortriterpenoids exhibit significant cell protecting activity against H_2O_2-induced PC12 cell damage.[8] Recently, in 2012, the same group isolated two more new C-24 nortriterpenoids walsucochinoids A (**1j**) and B (**1k**) from *Walsura cochinchinensis*.[9] Even though the bioactivities of this family of compounds have yet to be examined comprehensively, preliminary studies have revealed that pelorol (**1c**) is an activator of the Src *h*omology 2 domain containing *i*nositol 5-*p*hosphatase (SHIP),[10] whereas dasyscyphin B (**1e**) shows potent cytotoxic activities in several human cell lines[6a] and dasyscyphin D (**1f**) and E (**1g**) exhibit antifungal properties.[7]

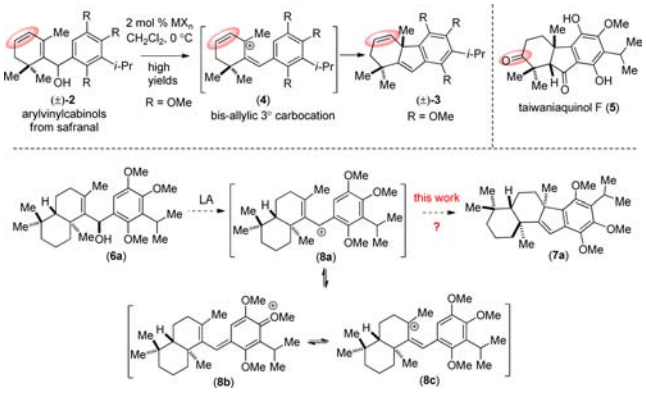
Despite the significant biological activities and the intriguing tetracyclic structure of these natural products, only a few syntheses have been reported in the literature. Prominent examples include Andersen's elegant approach of pelorol (**1c**) starting from (+)-sclareolide **9** (Scheme 1) via a key intramolecular Friedel–Crafts alkylation to create the cyclopentane C ring[11,12] total synthesis of dasyscyphin D (**1f**) by She[13] featuring a key $PtCl_2$-catalyzed pentannulation reaction and acid-catalyzed Robinson annulations,[13] a Diels–Alder approach by Alvarez-Manzaneda for first enantiospecific synthesis of akaol A (**1a**) from commercial (−)-sclareol,[14] and dasyscyphin B (**1e**) starting from commercial abietic acid.[15] In 2014, She et al. carried out the first asymmetric synthesis of walsucochin B (**1i**)[16] through a cationic polyolefin cyclization initiated by chiral epoxide.

Recently, our group reported an expeditious approach to the core structure of taiwaniaquinoids of type **3** through a Lewis acid catalyzed Nazarov-type cyclization of arylvinylcarbinols of

Received: February 16, 2016
Published: March 30, 2016

DOI: 10.1021/acs.orglett.6b00446
Org. Lett. 2016, 18, 1752–1755

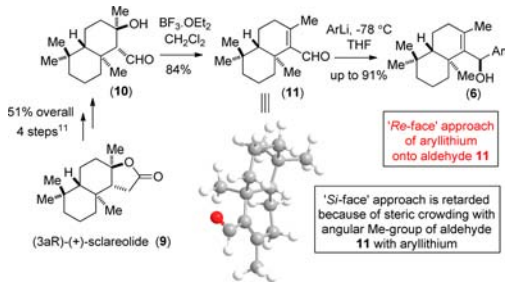
Scheme 1. Our Approach to Merosesquiterpenoids



type **2** (Scheme 1).[17] This reaction essentially goes through an intermediate bis-allylic carbocataion **4**. Utilizing this strategy, we demonstrated the first total synthesis of taiwaniaquinol F (**5**) (Scheme 1). Using similar arguments, herein we envisioned that arylvinylcarbinols of type **6** could efficiently be converted to carbotetracyclic framework such as **7a** via a key Nazarov-type cyclization (Scheme 1). Compound **7a** (Scheme 1) once formed, would provide opportunities to access total syntheses of various congeners of aforesaid merosesquiterpenoids. We hypothesized that arylvinylcarbinol **6a** would generate allyl benzyl carbocation species **8a** in the presence of Lewis acid, which would further be stabilized via **8b** and **8c**. Herein, we report an efficient route to access the tetracyclic core of merosesquiterpenes which is further utilized in the total synthesis of akaol A (**1a**) and related structures.

To this end, we synthesized a variety of arylvinylcarbinols of the type **6** utilizing a highly diastereoselective 1,2-addition of aryllithium onto a α,β-unsaturated aldehyde **11** (Scheme 2).

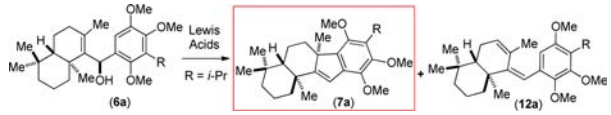
Scheme 2. Synthesis of Arylvinylcarbinols 6 from 9



This reaction afforded a single diastereomer via a "*Re*-face" approach of aryllithium.[18] As is evident from the energy-minimized structure of compound **11**, the "*Si*-face" approach is not favorable because of steric clash laid by the angular methyl group with the approaching aryllithium (Scheme 2). Aldehyde **11** can be synthesized from β-hydroxy aldehyde **10**[11] in the presence of $BF_3{\cdot}OEt_2$, which in turn could be accessed from (3a*R*)-(+)-sclareolide (**9**) in four steps in 51% overall yield (Scheme 2).

Next, we examined the Nazarov-type cyclization on the arylvinylcarbinol **6** in the presence of various Lewis acids in different solvents to construct the key carbotricyclic structure **7** as proposed. At the outset, we took compound **6a** as a model substrate to optimize the Nazarov-type cyclization in dichloromethane at room temperature using 5 mol % of variety of Lewis acids under open flask conditions (Table 1). Among various

Table 1. Selected Optimization of Nazarov-Type Reaction of 6a



no.	Lewis acid (mol %)	solvent	*T* (°C)	time (h)	yield (%) of **7a**[a,b]	yield (%) of **12a**[a,b]
1	$BF_3{\cdot}OEt_2$ (5)	CH_2Cl_2	25	0.5	27	60[c]
2	**$Sn(OTf)_2$ (5)**	**CH_2Cl_2**	**25**	**1**	**0**	**94**
3	$In(OTf)_3$ (5)	CH_2Cl_2	25	1	0	89
4	**$Bi(OTf)_3$ (5)**	**CH_2Cl_2**	**25**	**1**	**0**	**93**
5	$In(OTf)_3$ (2)	$(CH_2Cl)_2$	80	2	88	08
6	**$Sn(OTf)_2$ (2)**	**$(CH_2Cl)_2$**	**80**	**2**	**92**[d]	**0**
7	$Cu(OTf)_2$ (2)	$(CH_2Cl)_2$	80	2	71	18[c]
8	**$Bi(OTf)_3$ (2)**	**$(CH_2Cl)_2$**	**80**	**2**	**93**[e]	**0**

[a]Reactions were carried out on 0.25 mmol of (**6a**) in 3 mL of solvent. [b]Isolated yields reported after column chromatography. [c]Determined from ^{1}H NMR of impure materials. [d]Condition A (2 mol % of $Sn(OTf)_2$). [e]Condition B (2 mol % of $Bi(OTf)_3$).

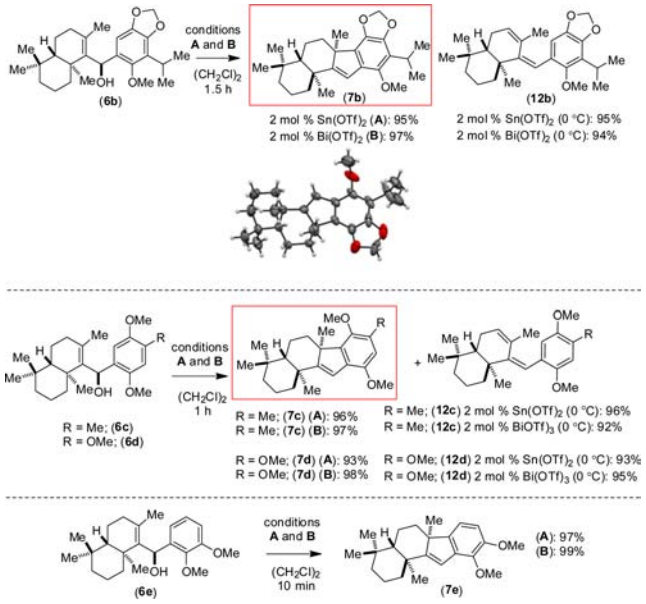
Lewis acids used, only $BF_3{\cdot}EtO_2$ could afford the carbotetracyclic core **7a** in just 27% along with the formation of 60% of diene (entries 1−4). It was observed that with 5 mol % of $Sn(OTf)_2$, $In(OTf)_3$ and $Bi(OTf)_3$ at room temperature, diene **12a** was formed exclusively with no traces of carbotetracyclic core **7a** (entries 2−4). Following exhaustive optimization (see the Supporting Information for details) it was found that 2 mol % of $Sn(OTf)_2$ and $Bi(OTf)_3$ at elevated temperature afforded compound **7a** as single diastereomer exclusively in 92 and 93% yields with no traces of diene **12a** (entries 5−8). In fact, the diene **12a** could be converted to **7a** under standard conditions.[19] This result indicated the intermediacy of carbocataion species **8a−c** in this Nazarov-type cyclization (Scheme 1).[19] On the basis of these optimization studies, it was decided to carry out further substrate scope using 2 mol % of $Sn(OTf)_2$ (condition A) and $Bi(OTf)_2$ in refluxing dichloroethane (condition B).

With the standard protocol in hand, we then probed few arylvinylcarbinols **6b−e** to construct carbotetracyclic cores **7b−e**, and the results are shown in Scheme 3. We could isolate carbotetracycles **7b−d** exclusively as single diastereomers in 93−98% yield from arylvinylcarbinols **6b−d**. As expected, 2 mol % of $Sn(OTf)_2$ and $Bi(OTf)_3$ at room temperature exclusively afforded diene**12b−d** in 92−96% yield (also see, entries 2−4, Table 1), whereas under optimized conditions A and B **6e** (Scheme 3) also afforded carbotetracycle **7e** as a single diastereomer exclusively in 99% yield with no traces of diene. The X-ray structure of one of the carbotetracycle **7b** unequivocally proved the formation of expected product (CCDC no. 1453267).

While arylvinylcabinols **6a−e**, having an alkyloxy group *ortho* to the reaction center, afforded a single diastereomer under standard conditions (Scheme 3), surprisingly, the reaction of arylvinylcabinols **6f−h** led to the formation of mixture of diastereomers **7f−h** and **13f−h** (dr ∼1.2:1) (Scheme 4). It was

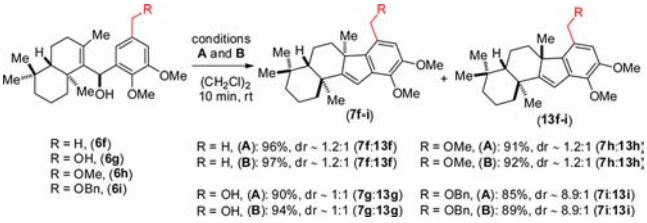
DOI: 10.1021/acs.orglett.6b00446
Org. Lett. 2016, 18, 1752−1755

Scheme 3. Nazarov-Type Reaction of Arylvinylcarbinols 6b[a]



[a]X-ray structure of **7b** (CCDC no. 1453267).

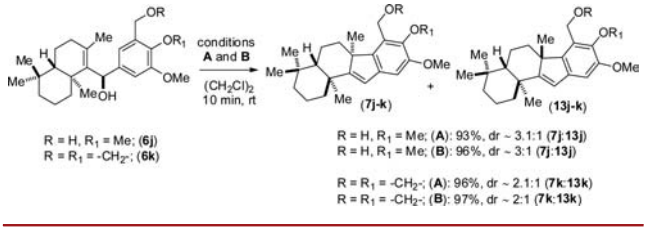
Scheme 4. Nazarov-Type Reaction of Arylvinylcarbinols 6f−i



found that the diastereoselectivity of these reactions very much depends on the sterics imposed by sp^3 carbon (highlighted in Scheme 4). In fact, benzyl ether protected substrate **6i** afforded diastereomers **7i** and **13i** in dr up to ∼8.9:1 (Scheme 4).[20]

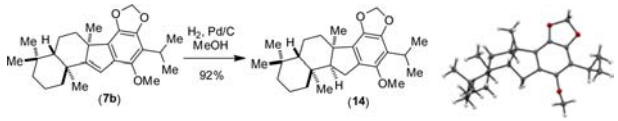
Later, in order to check the regioselective issues, if any, associated with this Nazarov-type cyclization, we further synthesized arylvinylcarbinols **6j,k** (Scheme 5). Arylvinylcarbinols **6j,k** afforded products in the form of a diastereomeric mixture due to approach of the aromatic ring from the *p*-position of the OMe group (Scheme 5). We speculate that the formation of diastereomers may be due to steric bias posed by the sp^3 carbon during the course of the reaction (Scheme 5).[20]

Scheme 5. Nazarov-Type Reaction of Arylvinylcarbinols 6j−k



Next, we were keen to elaborate the Nazarov cyclization products to synthetically useful intermediates. To this end, we hydrogenated carbotetracycle **7b** in the presence of Pd−C in MeOH under 1 atm of H_2 gas, which afforded tetracyclic compound **14** in 92% yield as single diastereomer (Scheme 6). The excellent diastereoselectivity observed was attributed to the

Scheme 6. Highly Diastereoselective Hydrogenation of Carbotetracycle 7b[a]

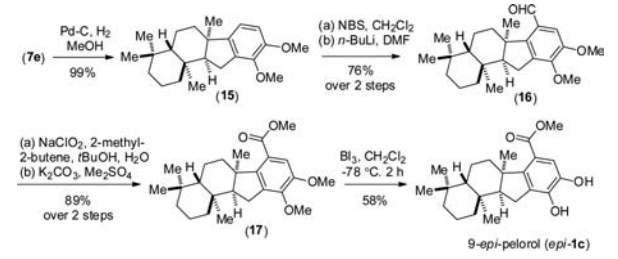


[a]X-ray structure of **14** (CCDC no. 1453268).

hydrogenation from the less hindered convex face of **7b**, which is quite clear from the X-ray crystal structure of **7b** (Scheme 3). Further, the X-ray crystal structure of compound **14** (CCDC no. 1453268) unambiguously proved the formation of the *cis*-fused indane ring (Scheme 6).

We applied this methodology in the total synthesis of 9-*epi*-pelorol (*epi*-**1c**) (Scheme 7). We began with hydrogenation of carbotetracycle **7e** which afforded saturated carbotetracycle **15** in quantitative yield as a single diastereomer.[21] This was then brominated with *N*-bromosuccinimide (NBS) followed by treatment with DMF in the presence of *n*-BuLi to afford carbotetracyclic aldehyde **16** in 92% yield (76% in overall two steps). Aldehyde **16** was then oxidized under Pinnick oxidation to afford carboxylic acid, which was further esterified, without purification, to obtain **17** in an overall 89% yield in two steps. Eventually, selective demethylation using BI_3 in dry dichloromethane at −78 °C afforded 9-*epi*-pelorol (*epi*-**1c**) in 58% yield (Scheme 7).

Scheme 7. Total Synthesis of Unnatural 9-*epi*-Pelorol (*epi*-1c)



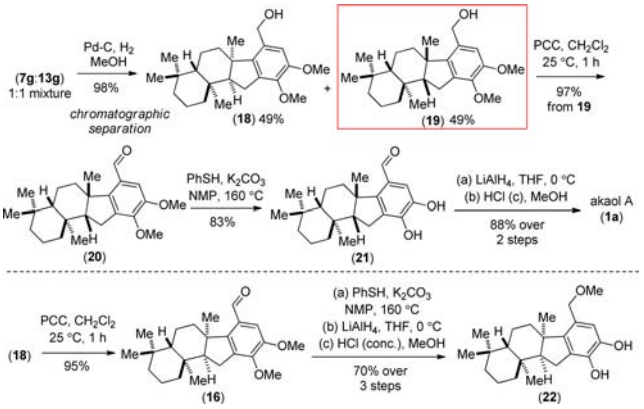
Later, we attempted the total synthesis of akalol A (**1a**) from **13g** (Scheme 4). Toward this end, we hydrogenated a mixture of **7g** and **13g** in the presence of Pd−C in MeOH under 1 atm of H_2 gas, which afforded chromatographically separable carbotetracycles **18** and **19**, respectively, in 98% yield in 1:1 ratio (Scheme 8).

Next, **19** was oxidized using PCC to furnish aldehyde **20** in 97%, which was then demethylated with PhSH in the presence of K_2CO_3 to afford aldehyde **21** in 83% yield. The later was then reduced with $LiAlH_4$ in THF followed by a chemoselective methylation of benzylalcohol with concn HCl in MeOH completed the total synthesis of akaol A (**1a**) in 88% yields over two steps (Scheme 8). Along a similar line, carbotetracycle **18** was converted to the unnatural sesquiterpene quinol **22** via aldehyde **16** in with similar efficiency (66.5% over four steps from **18**).

In conclusion, we have developed an efficient Lewis acid catalyzed Nazarov-type cyclization using only 2 mol % of $Sn(OTf)_2$ and $Bi(OTf)_3$ under mild conditions. A variety of

DOI: 10.1021/acs.orglett.6b00446
Org. Lett. 2016, 18, 1752−1755

Scheme 8. Total Synthesis of Merosesquiterpene Quinol Akaol A (1a)



enantioenriched carbotetracycles related to merosesquiterpenes were synthesized in good to excellent yields. The methodology provides a concise route to the marine sesquiterpene quinol akaol A (**1a**) in six steps from arylvinylcarbinol **6g** (32.6% overall yield) and 12 steps from easily available inexpensive (3a*R*)-(+)-sclareolide **9** (8.1% overall yield). We have also accomplished syntheses of unnatural sesquiterpene quinols 9-*epi*-pelorol (*epi*-**1c**) and **22** using the aforementioned methodology. Further application of this strategy to the total synthesis of complex merosesquitepenoids is under active investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00446.

Experimental procedures and analytical data (^{1}H, ^{13}C NMR spectra and HRMS) for all new compounds (PDF)

X-ray data for **7b** (CIF)

X-ray data for **14** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the BRNS, DAE, Government of India (Sanction No.: 2011/20/37C/12/BRNS/1731) and SERB, DST, Government of India (Sanction No.: SB/FT/CS-54/2011) are gratefully acknowledged. B.N.K., N.K., and P.K.M. thank the CSIR, New Delhi, for Senior Research Fellowships (SRFs). We sincerely thank the reviewers for their valuable suggestions to improve the manuscript.

■ REFERENCES

(1) (a) Cornforth, J. W. *Chem. Br.* **1968**, *4*, 102. (b) Geris, R.; Simpson, T. J. *Nat. Prod. Rep.* **2009**, *26*, 1063.

(2) Marcos, I. S.; Conde, A.; Moro, R. F.; Basabe, P.; Diez, D.; Urones, J. G. *Mini-Rev. Org. Chem.* **2010**, *7*, 230.

(3) Yong, K. W. L.; Jankam, A.; Hooper, J. N. A.; Suksamrarn, A.; Garson, M. J. *Tetrahedron* **2008**, *64*, 6341.

(4) (a) Goclik, E.; Koenig, G. M.; Wright, A. D.; Kaminsky, R. *J. Nat. Prod.* **2000**, *63*, 1150. (b) Kwak, J. H.; Schmitz, F. J.; Kelly, M. *J. Nat. Prod.* **2000**, *63*, 1153.

(5) Mukku, V. J. R. V.; Edrada, R. A.; Schmitz, F. J.; Shanks, M. K.; Chaudhuri, B.; Fabbro, D. *J. Nat. Prod.* **2003**, *66*, 686.

(6) (a) Rojas de la Parra, V.; Mierau, V.; Anke, T.; Sterner, O. *Tetrahedron* **2006**, *62*, 1828. (b) Mierau, V.; Rojas de la Parra, V.; Sterner, O.; Anke, T. *J. Antibiot.* **2006**, *59*, 53.

(7) Liermann, J. C.; Kolshorn, H.; Anke, H.; Thines, E.; Opatz, T. *J. Nat. Prod.* **2008**, *71*, 1654.

(8) Zhou, Z.-W.; Yin, S.; Zhang, H.-Y.; Fu, Y.; Yang, S.-P.; Wang, X.-N.; Wu, Y.; Tang, X.-C.; Yue, J.-M. *Org. Lett.* **2008**, *10*, 465.

(9) Han, M.-L.; Zhang, H.; Yang, S.-P.; Yue, J. M. *Org. Lett.* **2012**, *14*, 486.

(10) (a) Kalesnikoff, M.; Sly, L. M.; Hughes, M. R.; Buchse, T.; Rauh, M. J.; Cao, L.-P.; Lam, V.; Mui, A.; Huber, M.; Krystal, G. *Rev. Physiol. Biochem. Pharmacol.* **2004**, *149*, 87. (b) Rauh, M. J.; Kalesnikoff, M.; Hughes, M. R.; Sly, L. M.; Lam, V.; Krystal, G. *Biochem. Soc. Trans.* **2003**, *31*, 286. (c) Rauh, M. J.; Krystal, G. *Clin. Invest. Med.* **2002**, *25*, 68. (d) Krystal, G. *Semin. Immunol.* **2000**, *12*, 397.

(11) Yang, L.; Williams, D. E.; Mui, A.; Ong, C.; Krystal, G.; van Soest, R.; Andersen, R. *Org. Lett.* **2005**, *7*, 1073.

(12) For a two-synthon strategy involving the reaction of an aryl group with a bicyclic sesquiterpene in merosesquiterpene syntheses, see: (a) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (b) Alvarez-Manzaneda, E. J.; Chahboun, R.; Barranco Pérez, I.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R. *Org. Lett.* **2005**, *7*, 1477. (c) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Bouanou, H. *J. Org. Chem.* **2007**, *72*, 3332.

(13) Zhang, L.; Xie, X.; Liu, J.; Qi, J.; Ma, D.; She, X. *Org. Lett.* **2011**, *13*, 2956.

(14) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Fernández, A.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. M.; Akhaouzan, A. *Chem. Commun.* **2012**, *48*, 606.

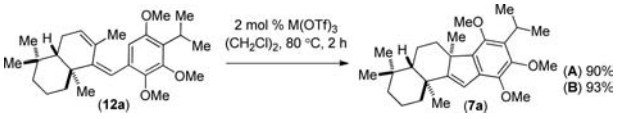
(15) Akhaouzan, A.; Fernández, A.; Mansour, A. I.; Alvarez, E.; Haidöur, A.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, E. *Org. Biomol. Chem.* **2013**, *11*, 6176.

(16) Xu, S.; Gu, J.; Li, H.; Ma, D.; Xie, X.; She, X. *Org. Lett.* **2014**, *16*, 1996.

(17) Kakde, B. N.; Kumari, P.; Bisai, A. *J. Org. Chem.* **2015**, *80*, 9889.

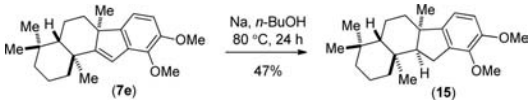
(18) Energy minimization (MM2) of α,β-unsaturated aldehyde**11** was performed using ChemBio 3D Ultra Version 12.0.

(19) Aryldiene**12a** can be efficiently converted to carbotetracyclic core **7a** in 90−93% isolated yields, indicating that Lewis acid catalyzed Nazarov-type cyclization probably goes through an aryl diene of type **12**.



(20) For torquoselectivity in Nazarov-type cyclizations, see: (a) Hutson, G. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 4988. (b) Denmark, S. E.; Wallace, M. A.; Walker, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 5543.

(21) Among various dissolving metal-mediated reductions attempted, Na in *n*-BuOH at elevated temperature afforded 47% yield of **15** from carbotetracycle**7e**.



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