JOC Article

Total Diastereofacial Selective Iodofunctionalization of Terpene Derivatives Based on Ipy_2BF_4

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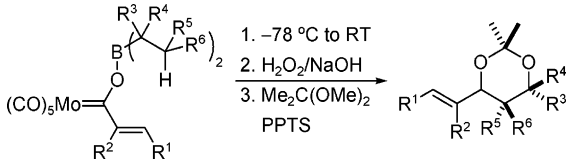
Acetonides **1**, easily obtained from simple terpenes, react with bispyridine iodonium (I) tetrafluoroborate (Ipy_2BF_4) and tetrafluoroboric acid in the presence of nucleophiles to give the corresponding adducts **2** with complete regio and diastereofacial control. Acetonides **1** containing a properly located phenyl or benzyloxy group easily undergo iodocyclization to furnish compounds **3** and **4**.

Introduction

Modern organic chemistry is focused on the search for new and efficient reactions to prepare polyfunctional compounds in an enantioselective manner.[1] Also, the application of methods and tools of organic chemistry to study biological problems is of great interest.[2] Among all the procedures, technologies, and strategies available, organometallic compounds have been widely applied to total synthesis as they allow access to complex frameworks of organic molecules in an easy way.[3] Recently,[4] we have disclosed an efficient and diastereoselective synthesis of 1,3-diols via an intramolecular C−H insertion reaction in boroxycarbene complexes (Scheme 1). Overall, this methodology results in a clear and efficient modification of terpenes in a regio- and diastereoselective manner.[5] Moreover, addition reactions to unsaturated systems promoted by halogens are valuable processes for the stereoselective functionalization of carbon−carbon double bonds.[6] In this context, many examples of diastereofacial selective iodocyclization reactions have been reported;[7] however, the related intermolecular version has been achieved with less success,[8] and in most of the cases, this reaction is circumscribed to the carbohydrate area.[9] Taking into account that terpenes play a central role in many biological processes[10] besides the importance of iodine-containing molecules in medicinal chemistry[11] made us to think that chiral iodine-containing compounds derived from terpenes could find application as biologi-

SCHEME 1. Conversion of Dialkylboroxycarbene Complexes into Acetonides by Sequential Intramolecular C−H Insertion Reaction and Oxidation



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‡ Departamento de Química Física y Analítica (X-ray service).

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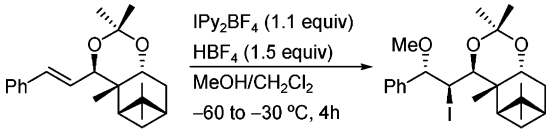
SCHEME 2. Diastereofacial Selective Addition of Methanol to Acetonide 1a Promoted by Ipy_2BF_4



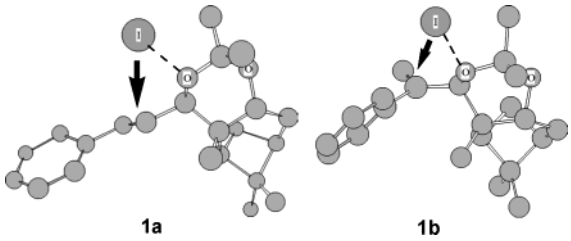
1a **2a**

cally active molecules. All these facts prompted us to investigate the convenience of using the reagent bispyridine iodonium (I) tetrafluoroborate (Ipy_2BF_4)[12] as a promoter to accomplish diastereofacial selective intermolecular iodofunctionalization reactions of unsaturated moieties derived from terpenes. On this basis, in this paper we describe a novel strategy to propagate the chirality of a terpene through the combination of the powerful chemistry of boroxycarbene complexes to activate C−H bonds with the ability of Ipy_2BF_4 reagent in addition reactions to unsaturated systems.

Results and Discussion

The acetonide **1a**, derived from (−)-α-pinene,[5] led to the exclusive formation of **2a** in 84% yield upon reaction from −60 to −30 °C with Ipy_2BF_4 (1.1 equiv) and tetrafluoroboric acid (1.5 equiv) in a solution containing a 3:1 mixture of dichloromethane/methanol, as depicted in Scheme 2. The structure and absolute configuration of the generated stereocenters of **2a** were unequivocally determined by NMR spectral analysis and confirmed by X-ray analysis.[13]

On this ground, we have explored the scope of this reaction by varying the nucleophile and the unsaturated system. The results are summarized in Table 1. Entries 1−4 correspond to the reaction of **1a** with different nucleophiles. Thus, to introduce the acetoxy group, a larger excess of acetic acid (1:1 mixture of dichloromethane/acetic acid) was used and the reaction was carried out at room temperature (entry 2). In the case of formation of azido derivative **2c**, an equivalent of trimethylsilyl azide was used as a nucleophile and boron trifluoride was used instead of tetrafluoroboric acid (entry 3).[14] To introduce the hydroxy group, a 1:1 mixture of dichloromethane/acetonitrile was used as a solvent and 6% of water was added. In this case, the reaction was carried out at room temperature and in the presence of air (entry 4). The amount of water should be carefully controlled to obtain the product **2d**. When an excess of water was used, a mixture of **2d** and the corresponding diol derived from the hydrolysis of the acetonide was noticed. In all of the cases examined (**2a**−**d**), single diastereoisomers were formed and their stereochemistries tentatively assigned on the basis of that firmly established for **2a**. From *ent*-**1a**, derived from (+)-α-pinene, was obtained *ent*-**2a** with good yield and again as a single stereoisomer (entry 5). The behavior of different terpene-based substrates was investigated using methanol as a nucleophile. The regio- and stereoselectivity of the reaction was tested on compounds **1b**−**d**, also derived from (−)-α-pinene. Under related conditions, **1b**,**c** led exclusively to adducts **2e**,**f**, respectively, corresponding to the Markonikov addition products as single diastereoisomers (entries 6 and 7). The complete regio- and diastereoselectivity observed in the reaction of **1d** to give **2g** (entry 8) are also remarkable. The structure of **2e**−**g** was determined by NMR experiments and, in the case of **2e**, was confirmed by X-ray analysis.[15] In the same way, acetonides **1e**−**g** derived from (+)-2-carene and (+)-3-carene, gave **2h**−**j**, respectively, through efficient and clean reactions as single diastereoisomers (entries 9−11).



1a **1b**

FIGURE 1. Model for the approach of iodonium ion to acetonides **1a** and **1b**.

The results described are fully compatible with an electrophilic addition process. An initial formation of a cyclic iodonium ion, followed by its subsequent capture by the nucleophile, led to the formation of anti adducts. The regiochemistry observed in the addition products is that expected for a process controlled by the electronic effects of the substituents. To account for the complete diastereofacial selectivity observed, it is reasonable to assume an initial coordination of the iodonium ion to the allylic oxygen of the acetonide, thus favoring the approach of the iodine atom to the same face of the olefin in which this oxygen is placed, as depicted in Figure 1 for compounds **1a** and **1b**.

The same iodofunctionalization reaction was attempted with acetonides **1h** and **1i**, derived from (−)-phenylapopinene[16] and (−)-myrtenol, respectively. However, treatment of **1h** with Ipy_2BF_4 and tetrafluoroboric acid in dichloromethane at room temperature, in the presence or absence of nucleophile, afforded the adduct **3** in 70% yield as a single diastereoisomer. Likewise, acetonide **1i** in similar reaction conditions gave rise exclusively to **4**[17] in 40% yield (Scheme 3). The structure and absolute configuration of the generated stereocenters of **3** were unequivocally determined by two-dimensional (COSY, HMQC, HMBC, and NOESY) NMR spectral analysis.[18]

(12) Ipy_2BF_4 is a commercial reagent from either Novabiochem or Aldrich. For a brief overall view on early applications, see: Barluenga, J. *Pure Appl. Chem.* **1999**, *71*, 431.

(13) Crystal data for **2a**: recrystallized from dichloromethane/chloroform 1:10, $C_{23}H_{33}IO_3$, M_r = 484.39, trigonal, space group $P3_2$, $a = b$ = 13.8260(9) Å, c = 10.0880(6) Å, V = 1670.1(2) Å^3, Z = 3, D_x = 1.444 Mg/m^3, Cu Kα radiation (λ = 1.54184 Å), μ = 11.436 mm^{-1}, T = 293 (2) K, final conventional R_1 = 0.041 and wR_2 = 0.1176 for 2389 reflections and 239 parameters. The absolute configuration was checked by refining the Flack parameter to χ = 0.007 (13).

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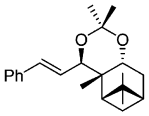
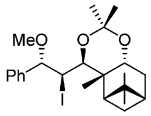
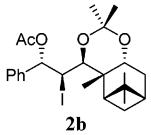
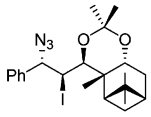
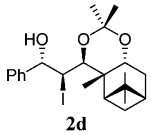
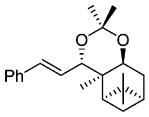
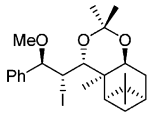
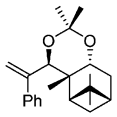
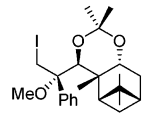
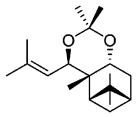
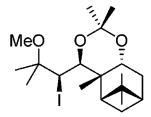
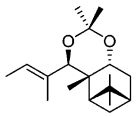
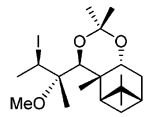
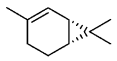
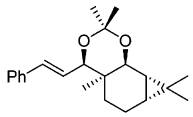
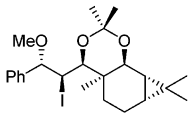
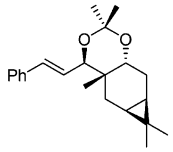
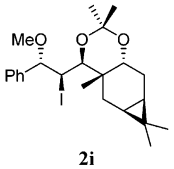
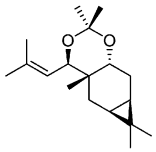
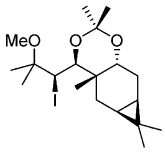
(15) Crystal data for **2e**: recrystallized from dichloromethane/chloroform 1:10, $C_{23}H_{33}IO_3$, M_r = 484.39, orthorhombic, space group $P2_12_12_1$, a = 8.47 (6) Å, b = 13.710 (15) Å, c = 19.471 (4) Å, V = 2260 (16) Å^3, Z = 4, D_x = 1.424 Mg/m^3, Mo Kα radiation (λ = 0.71073 Å), μ = 1.436 mm^{-1}, T = 293 (2) K, final conventional R_1 = 0.042 and wR_2 = 0.097 for 2860 "observed" reflections and 244 parameters. The absolute configuration was checked by refining the Flack parameter to χ = 0.03 (4).

(16) Brown, H. C.; Weissman, S. A. *J. Org. Chem.* **1990**, *55*, 1217.

(17) Debenzylation and related reactions promoted by Ipy_2BF_4 are subjects of study in our laboratory.

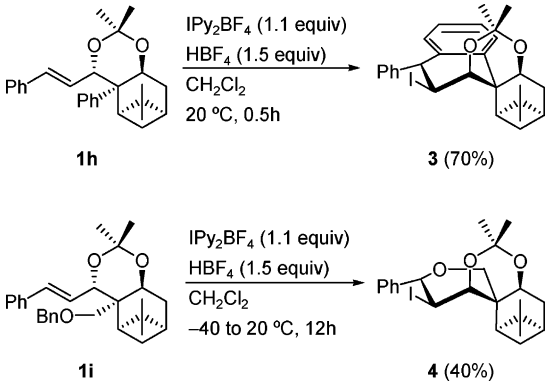
(18) Absolute configuration for **4** was assigned on the basis of that established for **3**.

TABLE 1. Diastereofacial Selective Iodofunctionalization Reaction of Terpene-Derived Alkenes Using Ipy_2BF_4

entry	terpene	starting material	nucleophile	product	Yield (%)[a]
1	 (−)-α-pinene	 **1a**	MeOH	 **2a**	84
2	(−)-α-pinene	**1a**	AcOH[b]	 **2b**	60
3	(−)-α-pinene	**1a**	$TMSN_3$[c]	 **2c**	78
4	(−)-α-pinene	**1a**	H_2O	 **2d**	66
5	 (+)-α-pinene	 ***ent*-1a**	MeOH	 ***ent*-2a**	82
6	(−)-α-pinene	 **1b**	MeOH	 **2e**	71
7	(−)-α-pinene	 **1c**	MeOH	 **2f**	82
8	(−)-α-pinene	 **1d**	MeOH	 **2g**	73
9	 (+)-2-carene	 **1e**	MeOH	 **2h**	82
10	 (+)-3-carene	 **1f**	MeOH	 **2i**	78
11	(+)-3-carene	 **1g**	MeOH	 **2j**	76

[a] Isolated yield based on acetonides **1**. [b] Mixture of dichloromethane/acetic acid (1:1) was used at room temperature. [c] $TMSN_3$ (1 equiv) and BF_3 instead of HBF_4 were used. [d] Mixture dichloromethane/acetonitrile (1:1) containing 6% H_2O was used at room temperature.

SCHEME 3. Diastereoselective Iodocyclization Reaction of 1h and 1i Promoted by Ipy_2BF_4



The formation of **3** could be easily explained by considering the iodocarbocyclization reaction in which the phenyl group in the quaternary center of **1h** acts as a nucleophile, in a process that is favored by the ideal location of the partners due to the terpene conformation.[7e,19] In the same way, compound **1i** could undergo an iodooxycyclization reaction with concomitant debenzylation reaction[20] leading to iodo derivative **4**. The absolute configuration of products **3** and **4** clearly indicate again that the reactions of **1h** and **1i** proceed in the same diastereofacially selective manner, that is, the iodonium ion attacking the face of the olefin where the allylic oxygen of the acetonide is placed.

Conclusions

We have described a simple and efficient strategy to generate highly polyfunctional compounds in a diastereoselective way by means of a new reaction sequence based on the combination of the unusual and diastereoselective activation of terpenes (via C−H insertion) with the use of Ipy_2BF_4 as a useful promoter of valuable iodofunctionalization reactions. The presence of a phenyl or benzyloxy group placed in a well-defined position of the starting terpene-derived actonide gives rise to complex cyclic molecules via diastereoselective iodocyclization reactions. Having in mind that the highly functionalized iodine containing products here described could be of biological interest, it should be noted that the process allows for the synthesis of many structurally diverse analogues, as different building blocks can be varied (starting terpene, side chain, nucleophile). All of these issues and the potential of the products as chiral ligands in organometallic chemistry are objects of study in our laboratories.

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Supporting Information Available: Full experimental details and spectroscopic data, X-ray crystal structure of **2a** and **2e** (ORTEP, thermal ellipsoids), and tables of the crystal data and structure refinement, atomic coordinates, bond lengths, bond angles, isotropic displacement parameters, hydrogen coordinates, and torsion angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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