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# A Diastereoselective Switch in the Access to Isobenzofuran-Derived α-Selenoesters

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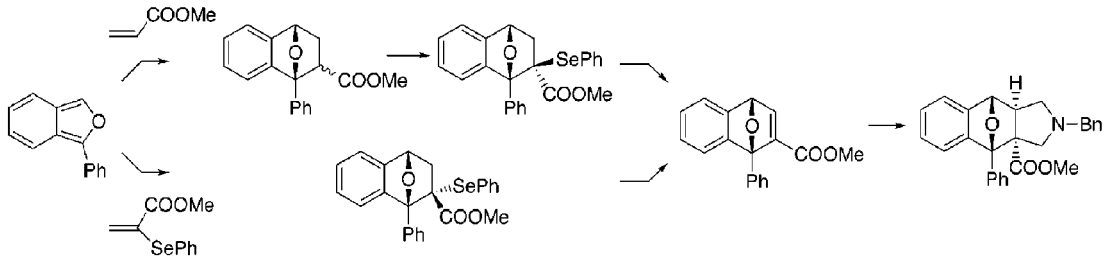
## ABSTRACT




**The cycloaddition of 1-phenylisobenzofuran (PIBF) with methyl acrylate yields, in a moderate endo/exo ratio, the expected oxa-bridged adduct, which can be deprotonated and condensed on diphenyl diselenide to provide, in a stereoconvergent step, the "endo" α-selenoester. Its "exo" epimer is obtained by reacting PIBF and methyl α-phenylselenoacrylate. These adducts can be oxidized to give a common unsaturated bridged ester that can react with an imminium ylide to provide the expected pyrrolidine stereoselectively.**

Farnesyltransferase inhibitors have opened promising new directions in cancer therapy lately, particularly in the case of tumors associated to Ras protein mutations.[1] The polycyclic inhibitor RPR 115135, which exhibits remarkably low geranylgeranyltransferase inhibition profiles while keeping significant in vivo activities,[2] constitutes a particularly inspiring starting point for a focused study on the structure−activity relationship in the benzo[*f*]perhydroisoindole (BPHI) series. The possible importance of both the carbon bridge in the BPHI structure and the position of the ester group for the drug−enzyme interaction made analogue **1** an appealing targets. Unsaturated ester **2** cannot be prepared by a direct cycloaddition between 1-phenylisobenzofuran **5** and methyl propiolate which, under classical thermal conditions, instead leads to a complex mixture of unidentified compounds.[3] Thus, an alternative retrosynthetic approach of the polycyclic skeleton is disclosed in Figure 1. The pyrrolidine ring in **1** can result from a 1,3-dipolar cycloaddition between **2** and Sakurai's dipole.[4] The synthesis and oxidation of the corresponding α-selenoesters **3** thus offered an alternative route to **2**. We describe here two methods giving a totally stereoselective access to both isomers of the key intermediate **3**.

Selenoesters such as **3** are classically prepared by deprotonation and selenation of the corresponding esters. In our

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(1) Bos, J. L. *Cancer Res.* **1989**, *49*, 4682.

(2) Mailliet, P.; Laoui, A.; Bourzat, J. D.; Capet, M.; Chevé, M.; Commerçon, A.; Dereu, N.; Lebrun, A.; Martin, J. P.; Peyronel, J. F.; Salagnad, C.; Thompson, F.; Zucco, M.; Guitton, J. D.; Pantel, G.; Bissery, M. C.; Brealey, C.; Lavayre, J.; Lelièvre, Y.; Riou, J. F.; Vrignaud, P.; Duchesne, M.; Lavelle, F. In *Farnesyltransferase and Geranylgeranyltransferase Inhibitors in Cancer and Cardiovascular therapy*; Sebte, S., Ed.; Humana Press: Totowa, NJ, in press.

(3) Martin, C.; Mailliet, P.; Maddaluno, J. Full paper in preparation.

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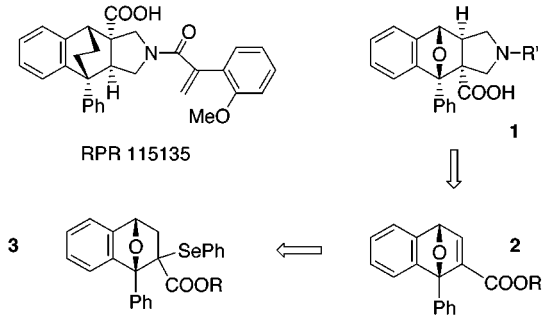
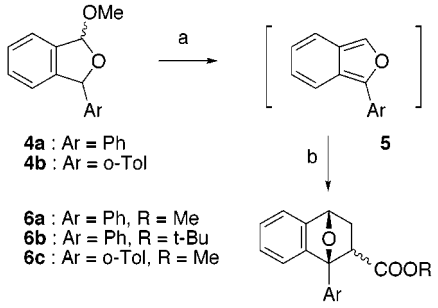



**Figure 1.** Retrosynthetic route to inhibitor analogue **1**.

case, the precursor **6** (Scheme 1) has been obtained by a [4 + 2] cycloaddition between 1-phenylisobenzofuran **5** and acrylates. PIBF **5** itself was handily prepared in situ by *n*-butyllithium-induced *δ*-elimination[5] on phthalane **4**.[6]

**Scheme 1**[a]




[a] (a) 2 equiv of n-BuLi, $Et_2O$, rt, 15 min then t-BuOH quench; (b) methyl or *tert*-butyl acrylate, THF, rfx, 2 h.

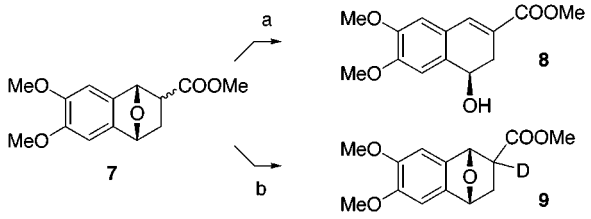
The thermal cycloaddition of **5** with methyl acrylate provided **6** as a single regioisomer but as a 38:62 endo/exo mixture of stereoisomers.[7] The regioselectivity was as expected given previous results on related systems obtained by Gilchrist[8] or, more recently, by Iwasaki[9] and fit our own AM1 calculations on the HOMO coefficients of **5**.[3]

Because the lack of endoselectivity of this step is possibly a drawback for the selenation, we tried to further tune a few structural parameters. However, when replacing the phenyl group by an *o*-tolyl group, the selectivity is marginally affected (44:56 in favor of exo **6c**); resorting to *tert*-butyl acrylate hardly reverses this ratio (57:43 in favor of endo[10] **6b** this time).

(5) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3849.
(6) Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 534.
(7) An exo-preference has been reported for similar systems. See for instance: (a) Nozaki, H.; Yamaguti, T.; Ueda, S. Kondo, K. *Tetrahedron* **1968**, *24*, 1445. (b) Hickmott, P. W.; Simpson, R. *J. Chem. Soc. (C)* **1972**, 302. (c) Rodrigo, R.; Knabe, S. M. *J. Org. Chem.* **1986**, *51*, 3973.
(8) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 336.
(9) Sugahara, M.; Moritani, Y.; Terakawa, Y.; Ogiku, T.; Ukita, T.; Iwasaki, T. *Tetrahedron Lett.* **1998**, *39*, 1377.

The deprotonation step in the α position of such an oxa-bridged system could also be troublesome. Rodrigo et al. have indeed shown that the deprotonation of ester **7** by LDA triggers an instantaneous opening of the bridge, leading to alcohol **8**.[11] However, the same authors have shown that if the deprotonation takes place in the presence of an electrophile such as $D_2O$, the α-deuterated bridged esters **9** are recovered in almost quantitative yields (Scheme 2).

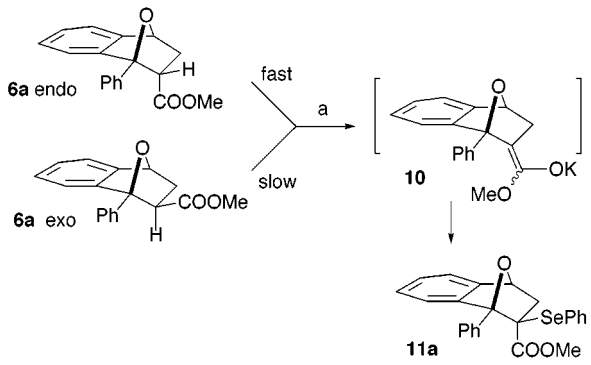
**Scheme 2**[a]




[a] (a) LDA, THF, 0 °C; (b) MeONa, MeOD, 20 °C.

In our case, LDA appeared rather inefficient, the starting esters **6** being recovered unaltered. By contrast, KHMDS yielded the expected selenoester provided that diphenyl diselenide was added to the medium before deprotonation (Scheme 3). It is worth noting that both **6a** and **6b** lead to

**Scheme 3**[a]




(a) 2 equiv of $(PhSe)_2$ and then 2 equiv of KHMDS, THF, rt.

the same "endo" epimer **11a**. However, the kinetics of their transformation are rather different: after 30 min at room temperature, the reaction is total with **6a** while the conversion hardly reaches 40% with **6b**; the relative ease of access to the acidic proton in **6a** and **6b** are probably at the origin of this phenomenon.

The mixture of **6** isomers can, of course, be treated without prior separation provided that the reaction time is long enough. The stereoconvergence of the selenation is likely due to the intermediate formation of the same (except,

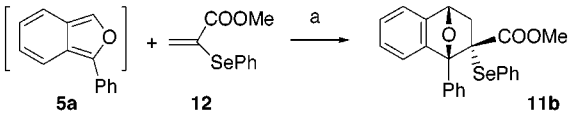
(10) As expected according to Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 17−22.
(11) Keay, B.; Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 1093.

eventually, for the *E*(O)/*Z*(O) ratio) potassium enolate **10**, which reacts with the electrophile on its only accessible convex face. Thus, the selenoester is finally obtained as a single diastereomer **11a** (bearing the ester group endo). This compound appeared relatively unstable on silica gel and is therefore difficult to purify under standard chromatographic conditions. It can, however, be used as a crude mixture in the following oxidation step. This instability could be related to the steric constraints introduced by the selenium atom; adduct **6b** was also observed to be much more difficult to purify by chromatography than its analogue **6a**.

Resorting to α-phenylselenyl methyl acrylate **12** offered an attractive shortcut in our retrosynthetic route since its cycloaddition with PIBF **5a** would yield selenoester **11** directly. The starting selenoacrylate **12** has been synthesized according to the procedure described by Piettre and colleagues,[12] which consists of the reversible addition of PhSeCl to methyl acrylate in the presence of $ZnCl_2$. Upon basic quenching ($NEt_3$) only the captodative gem-disubstituted regioisomer is obtained in 82% yield.

The cycloaddition was performed between **5a**, generated in situ as described above, and **12** in toluene at 80 °C for 2 h (Scheme 4). A single adduct **11b** was recovered. The NMR

**Scheme 4**[a]




[a] (a) Tol, 80 °C, 2 h.

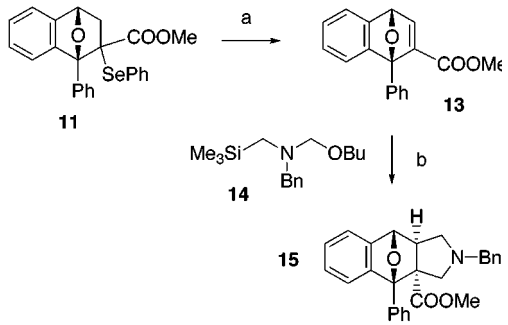
showed that the regioselectivity was unchanged while the exo selectivity became total this time. This dramatic preference can be tentatively attributed to $\pi-\pi$ interactions between the phenyl group borne by the selenium in **12**, and the conjugated cyclohexadienic system in **5a**. Because isomer **11b** is also very sensitive to silica gel, probably for steric reasons comparable to those described above, its chromatographic yield plummets to impractical values.

The next step toward **2** was the oxidation of **11** into the corresponding epimeric selenoxides, which is expected to undergo an instantaneous $\beta$-elimination of selenenic acid since the selenium atom is syn to a proton in both **11a** and **11b**. Thus, hydrogen peroxide has been reacted separately with the two epimers of **11** at −40 °C, giving in both cases the expected bridged ethylenic ester **13** (Scheme 5). Albeit the NMR spectra of the reaction mixture leaves no doubt to the structure of the product, this compound is as sensitive to silica gel as its precursors, preventing its chromatographic purification and the evaluation of the yield. A facile retro-Diels−Alder reaction, previously observed for a carbon-bridged precursor of RPR 115135,[13] probably explains this instability.

(12) Piettre, S.; Janousek, Z.; Merenyi, R.; Viehe, H. G. *Tetrahedron* **1985**, *41*, 2527.

(13) Mailliet, P. Unpublished results.

**Scheme 5**[a]




[a] (a) $H_2O_2$, $CH_2Cl_2$, −40 °C; (b) 0.1 equiv of $CF_3COOH$, $CH_2Cl_2$, rt.

The [3 + 2] cycloaddition between crude **13** and the dipole derived from amine **14** has been achieved under acidic conditions (Scheme 5).[4b] The pyrrolidine **15** was obtained as a single diastereomer, possessing an endo ester appendage.[14] This selectivity makes sense in regards to the folded structure of **13**, which presents a single convex face accessible to the dipole (Figure 2). This final adduct was purified by chromatography and recovered in 14% overall yield from **4a** (four steps).

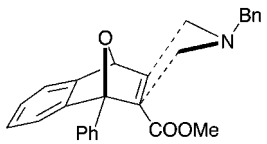



**Figure 2.** Approach of the ylide along the convex face of **13**.

In conclusion, this preliminary study on the synthetic routes to pyrrolidine **15** provides evidence for a diastereomeric switch that allows for a selective access to both epimers of α-selenoester **11**. These two isomers give the same 1,4-epoxy-1,4-dihydronaphthalene **13** after $H_2O_2$ oxidation; their different topologies could possibly be exploited through radical chemistry. This selectivity, which seems mainly governed by the marked concavity of the oxa-bridged skeleton, could also be extended to other electrophiles. All details on the developments brought about by the synthesis of these and others farnesyltransferase inhibitors analogues will be reported in a full paper.[3]

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(14) $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ (ppm) 2.27 (1H, d, $J$ = 9.6), 2.35 (1H, t, $J$ = 8.1), 3.20 (1H, t, $J$ = 7.9), 3.34 (1H, d, $J$ = 7.9), 3.40 (3H, s), 3.48 (1H, d, $J$ = 9.5), 3.56 (2H, s), 5.22 (1H, s), 6.94−7.77 (14H, m); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ (ppm) 52.02, 54.82, 58.28, 59.71, 59.91, 66.27, 81.06, 92.94, 119.29, 120.43, 126.57, 126.84, 127.06, 127.22, 127.87, 128.15, 128.38, 136.00, 138.63, 144.87, 145.83, 173.83; CIMS (i-BuH) *m*/*z* 412 (M + 1, 100); exact mass calcd for $C_{27}H_{26}O_3N$ *m*/*z* 412.1913, found 412.1913.