Pergamon

Tetrahedron Letters 42 (2001) 4111–4113

TETRAHEDRON LETTERS

Regioselective lithiations of a pterocarpan skeleton: the first synthesis of (±)-4′-dehydroxycabenegrin A-I

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Received 29 March 2001; accepted 24 April 2001

Abstract—Maackiain *O*-MOM derivative **3b** was regioselectively lithiated at the C-10 position of D-ring and reacted with electrophiles. Regioselective lithiation of the C-10 TMS-substituted derivative **5d**, followed by organocopper formation and treatment with prenyl bromide, enabled the desired prenylation at C-4. The obtained compound **6d** was employed in the first synthesis of racemic 4′-dehydroxycabenegrin A-I, **4**. Moreover, dialkylation of **3b** at the two most reactive sites could be effected through the generation of a dilithiated species. A preliminary result dealing with diethylcarbamate derivative **3c** is also shown.

Pterocarpans, members of the isoflavonoid family of natural products, show a variety of substitution patterns at rings A and D. For instance, Cabenegrins A-I (**1**) and A-II (**2**) (Fig. 1), prenylated at different positions of ring A, were isolated by Nakanishi and co-workers[1] from a Brazilian folk medicine known as *Específico Pessoa*. Both compounds were tested separately and showed significant anti-snake venom activity. Silveira and co-workers[2] have recently isolated, among other substances, novel pterocarpan 4′-dehydroxycabenegrin A-I, **4**, from the roots of *Harpalyce brasiliana* (*erva-de-cobra*), employed by Brazil's northeast populations against snake bites. So far, this substance has not been submitted to biological evaluations by other groups.[3]

The literature procedures for construction of substituted isoflavonoids,[4] especially those where substituent incorporation is carried out at late stages in the synthesis, are neither efficient nor practical. Therefore, we decided to investigate the possibility of accomplishing efficient substitutions on pterocarpan skeletons via regioselective lithiations of such structures bearing strong directing *o*-metallation groups (DMGs),[5] a not attained task. In this letter, we describe our study on DMG-directed lithiations of a pterocarpan skeleton, namely maackiain derivative **3b**, carrying the methoxymethyl (MOM) group protecting the hydroxyl group. A novel methodology emerged from this effort, which has been applied to the first synthesis of natural product **4**. In addition, a preliminary result concerned with the lithiation of carbamate derivative **3c** is shown.

Substance (±)-**3a** (Fig. 1) was prepared from resorcinol and sesamol as previously described.[6] Transformation of **3a** into *O*-substituted derivatives **3b**[5c] and **3c**[5d] was accomplished by standard procedures. At that point, we envisioned that we might be able to carry out selective deprotonation at C-4, due to the presence of

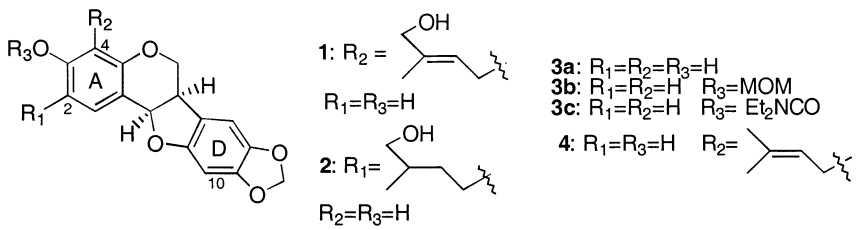

Figure 1.

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PII: S0040-4039(01)00682-7

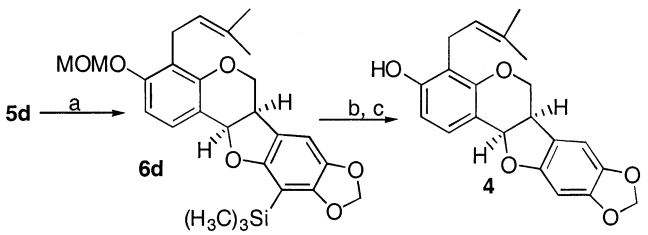
the MOM group at ring A. Reaction of **3b** with BuLi in THF followed by addition of D_2O led to **5a** only (Scheme 1), disclosing the C-10 position as the most kinetically acidic. Treatment of the involved aryl lithium intermediate with prenyl bromide, benzyl bromide or TMSCl led to compounds **5b**, **5c** or **5d**, respectively.

The observed deprotonation regioselectivity in these reactions, favouring position 10 over position 4, is surprising as the MOM group is recognized as a stronger directing metallation group (DMG) than alkoxyl groups.[5c] We tentatively point out that strong inductive effects, associated with higher oxygenation (as shown by the D-ring), may override other aspects involved in the lithiation mechanism, such as lithium atom complexation (supposedly, more efficient with MOM group).[7] Simultaneous disubstitution on **3b** at C-4 and C-10 could be achieved via the intervention of a dilithiated intermediate (Scheme 1). Reaction of this species with prenyl bromide, benzyl bromide or TMSCl afforded compounds **6a**, **6b** or **6c**, respectively, in good yields (Scheme 1). Finally, removal of the MOM protecting group on substances **5** and **6** (PPTS, ^{i}PrOH, reflux)[8] leading to the corresponding phenols **7**[9] and **8**, occurred uneventfully (Scheme 2).

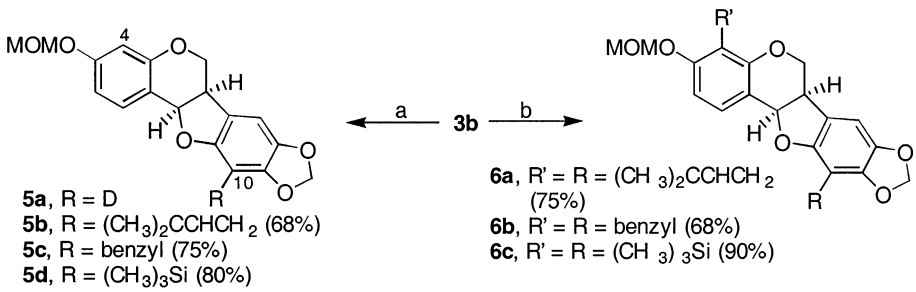
As long as the selective deprotonation at C-4 and C-10 and cleavage of the MOM group were shown to be feasible, we pursued the synthesis of natural product **4**. Compound **5d** (Scheme 3) bearing the removable TMS group at D-ring might be useful in the preparation of pterocarpans substituted at the C-4 position. Thus, this substance underwent selective metallation at C-4. Treatment of the resulting aryllithium species with prenyl bromide (rt, reflux) led to compound **6d** (40–50% yield), along with at least two other by-products of difficult separation (Scheme 3). This result is quite remarkable if one takes into account the good yields of compounds **5b**, **5d**, **6a** and **6c**, achieved under the same conditions.[8] As a matter of fact, we were able to produce **6d** in a cleaner fashion by transmetallating the organolithium intermediate to an organocopper species before the addition of the electrophile. Desilylation of this substance followed by cleavage of the MOM group afforded (±)-4′-dehydroxycabenegrin A-I, **4** (40%, two steps). All physical data of the synthetic sample were consistent with those of the natural material.[2] The possibility of introducing the prenyl group or oxygenated counterparts under mild conditions with high regioselectivity and at latter stages in the synthesis makes this method particularly attractive.[10]

We have also attempted to selectively deprotonate the C-4 position of A-ring avoiding the need for blocking position 10. Therefore, we turned our attention to the lithiation of maackiain derivative **3c**, carrying the diethyl carbamate group at C-3, a much stronger DMG.[5b,d]

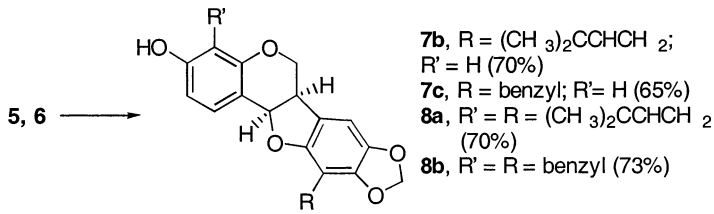
As a preliminary assay, this compound was deprotonated with the ^{s}BuLi/TMEDA system[5d,11,12] and reacted with MeI (Scheme 4). Regioisomers **9a** and **9b** along with dimethylated maackiain derivative **10** were



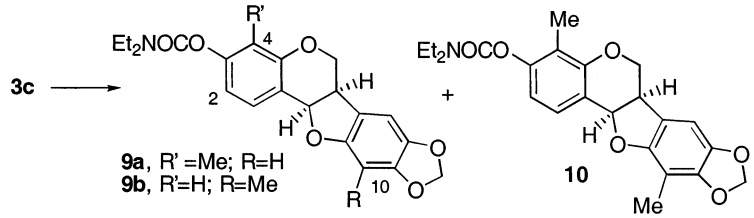
Scheme 3. *Conditions*: (a) i. BuLi, THF, 0°C, 40 min; ii. CuI (1.3:1), −78 to −40°C; iii. prenyl bromide −78°C–rt. (b) TBAF·nH$_2$O, THF, H$_2$O (2 mol equiv.), rt. (c) PPTS (0.2 mol equiv.), ^{i}PrOH, 80°C.



Scheme 1. *Conditions*: (a) i. BuLi (1.0–1.2 equiv.), THF, 0°C, 40 min; ii. electrophile, rt, reflux (2 h) (except for D_2O: rt); (b) the same conditions, except for BuLi (2.4 equiv.).



Scheme 2. *Conditions*: PPTS (1.2 equiv.), ^{i}PrOH, reflux.



Scheme 4. *Conditions*: ^{s}BuLi (1.2 equiv.), TMEDA, THF, −78°C, 1 h; ii. MeI, −78°C–rt.

formed, as a not resolved mixture, in a 58:15:27 ratio (GC–MS), respectively (Scheme 4). The identity of the major monomethylated product **9a** was assigned through a long-range ^{1}H,^{1}H COSY experiment on the mixture, which indicated a correlation of the higher intensity methyl signal with the C-2 hydrogen signal. The same was not observed with the lower intensity methyl signal. The ratio of monoalkylated products shows that the diethyl carbamate group actually enabled a rather satisfactory reversal of regioselectivity. However, the formation of significant amounts of products resulting from disubstitution, in this case **10**, is likely to preclude the synthetic use of **3c** for selective substitution at C-4, at least under the conditions tested so far. It is noteworthy that our lithiation experiments with maackiain derivatives enabled an unprecedented comparison of the acidity of resorcinol-derived moieties (ring A) bearing efficient DMGs and sesamol-derived moieties (ring D). The latter ones proved to be highly competitive. The exploration of these results in total synthesis of other natural products, as well as the lithiation of pterocarpan skeletons of different oxygenation patterns bearing MOM and diethylcarbamate DMGs are currently under investigation.

Acknowledgements

The authors thank PRONEX, CNPq and FUJB-UFRJ for the research grants; FAPERJ (fellowships to A.L.C. and A.J.M.S.), Central Analítica-NPPN for analytical data, Instituto de Química-UFRJ for IR spectra.

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