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"Me_3Al-$TMSOSO_2CF_3$" A New Reagent for Conversion of Carbonyl to Geminal Dimethyl Functionality: Regiospecific Synthesis of Alkylated A Ring of Arotinoids

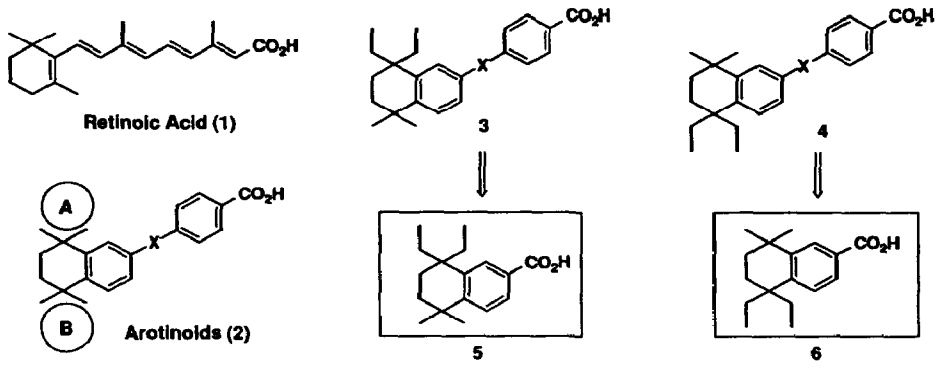
Choung Un Kim*, Peter F. Misco, Bing Y. Luh and Muzammil M. Mansuri

Bristol-Myers Squibb Pharmaceutical Research Institute
5 Research Parkway, Wallingford, Connecticut 06492

ABSTRACT: Regiospecific synthesis of alkylated A ring of arotinoids has been achieved by using Me_3Al-$TMSOSO_2CF_3$ as a key reagent for conversion of carbonyl to a geminal dimethyl functionality.

Retinoic acid plays a fundamental role on cell growth and differentiation through activating retinoic acid receptors (RARs). Three subtypes of these receptors, RAR-α, RAR-β and RAR-γ have been identified [1] An additional family of receptors called RXR has also recently been discovered.[2] Those receptors are located in the nucleus of the cell and modulate gene transcription by ligand-dependent binding. However, the role of the various RARs in exerting any specific biological response is still not well defined. Therefore, there is considerable fundamental interest in developing compounds that selectively activate one of the RARs, thereby enabling us to investigate the role of an individual receptor in regulating the biological activity. Among many retinoic acid analogues, the aromatic analogues **2** (arotinoids) of retinoic acid transactivated RARs and exhibited biological activities similar to retinoic acid.[3] The structure-activity relationship study revealed that the lipophilic change in the A ring of arotinoids **2** resulted in the profound difference in their biological activity.[4] Therefore, in order to investigate the structural requirements of arotinoids **2** for the selective transactivation of RARs, we have decided to modify systematically the lipophilic regions, A and B of arotinoids (**2**) as shown in Chart I. For this purpose, as exemplified for the synthesis of diethyl analogues **3** and **4**, it is required to devise the regiospecific synthesis of intermediates **5** and **6** that could be transformed to **3** and **4** by the chemistry developed for **2** [5]

Chart I



Central to the development of the synthetic route to **5** is the issue of the regioselectivity of constructing the unsymmetrically alkylated cyclohexane ring. As illustrated in Scheme I, the Friedel-Crafts coupling of succinic anhydride and toluene gave exclusively the para isomer **7**. Exposure of **7** to methylmagnesium chloride (1 equiv) gave lactone **8** in high yield. Many attempts to convert **7** or **8** to the geminal dimethyl analogue **9** (or **10**) by known methodologies including $MeTiCl_3$[6], Me_2TiCl_2[7], Me_2Zn[8] and Me_3Al[9] were not successful due to the formation of various products. Finally, when lactone **8** was treated with "Me_3Al-$TMSOSO_2CF_3$" (1 equiv each) in CH_2Cl_2 the desired dimethyl product **9** was obtained in almost quantitative yield.[10] Interestingly, the keto intermediate **7** was also converted directly to **9** with "Me_3Al-$TMSOSO_2CF_3$" (2:1) probably via the intermediate **8**.

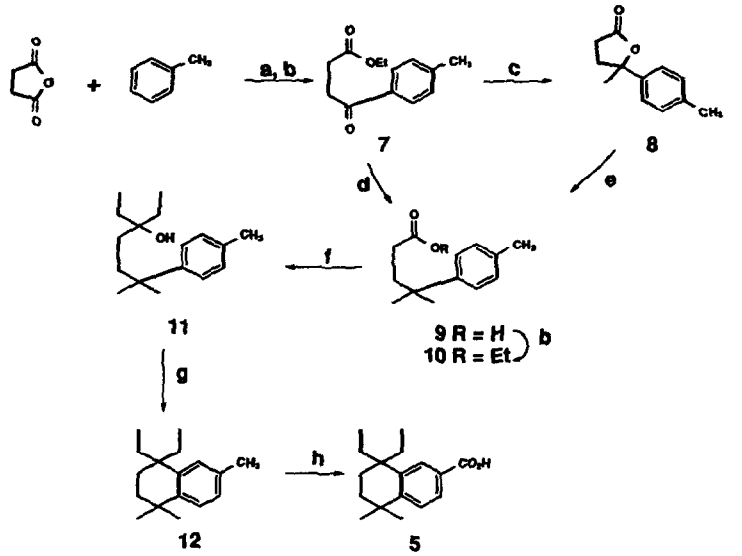
Synthesis of 9 from 7: To a cooled (0°C) solution of **7** (1.1g, 5 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of 2M Me_3Al in hexane (5 mL, 10 mmol) followed by a dropwise addition of $TMSOSO_2CF_3$ (1 mL, 5 mmol) under argon atmosphere. The solution was allowed to stand at room temperature for 15 h. The reaction was then poured into a mixture of ether - ice water and the solution was acidified with 40% H_3PO_4. The ether layer was separated, washed with brine, dried ($MgSO_4$) and evaporated in vacuo to dryness to give 980 mg (95%) of **9** as a colorless oil (~ 100% pure by NMR).

At the moment, the general scope of this new reagent for the synthesis of the geminal tertiary carbon from the keto functionality remained to be investigated. Further conversion of **9** to **5** was achieved by the sequence (1) esterification of **9** to **10**; (2) addition of ethylmagnesium chloride (2 equiv) to **10** to generate **11**; (3) Friedel-Crafts cyclization of **11** to **12** with conc H_2SO_4; (4) $KMnO_4$ oxidation of **12** to generate **5**.

Next, we turned our attention to the synthesis of **6**. Our initial approach to the synthesis of **6** began with the addition of ethylmagnesium bromide (1 equiv) to the keto intermediate **7** that gave lactone **13** in high yield. Addition of Et_3Al-$TMSOSO_2CF_3$ to **13** produced a mixture of **14** and **15** in a ratio of 2:1. Unfortunately, the reductive product **15** or its derivatives (e.g. ester, amide) were unable to be separated from **14** under various purification methods. Therefore, we turned to an alternative method for accomplishing the regioselective synthesis of **6**. The organo zinc agent **17** generated from the lithium salt of **16** condensed with acid chloride **18** to give the keto intermediate **19** in good yield. Upon treatment with "Me_3Al-$TMSOSO_2CF_3$" in CH_2Cl_2 at 0°C, **19** provided the geminal dimethyl intermediate **20** in almost quantitative yield.

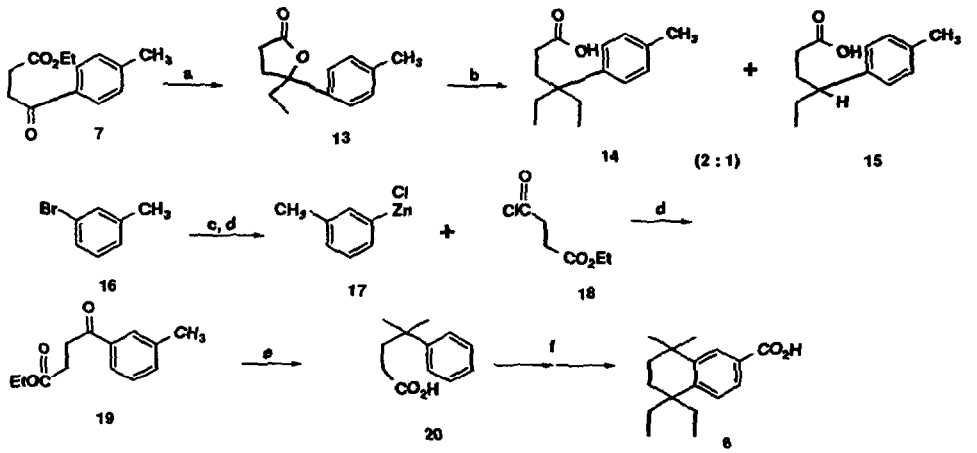
The successful approach described herein, enabled us to synthesize a number of alkylated and arylated analogues related to the A and B region of the arotinoid A ring depicted in structure 2. The structure-activity relationships of those derivatives and their ability to transactivate RARs selectively will be reported in a future publication.

Scheme I



a: $AlCl_3$, $PhCH_3$, 60°C, 60 min., 92%; b: EtOH, HCl, 25°C, 15h, 95%; c: CH_3MgBr (1 equiv), Et_2O, -40°C, 30 min. 90%; d: Me_3Al-$TMSOSO_2CF_3$ (1:1, 2 equiv), CH_2Cl_2, 0°C → 25°C, 15 h, 95%; e: Me_3Al-$TMSOSO_2CF_3$ (1:1, 1 equiv.), CH_2Cl_2, 0°C → 25°C, 15 h, 95%; f: EtMgBr (2 equiv) Et_2O, -70°C, 60 min, 85%; g: conc H_2SO_4, 0°C, 30 min. 75%; h: $KMnO_4$ (4 equiv), NaOH (2 equiv), pyridine-water (3:1), 95°C 15 h, 70%.

Scheme II



a: EtMgBr (1 equiv), Et_2O, -30°C, 85%; b: Et_3Al-$TMSOSO_2CF_3$ (1:1, 1 equiv), CH_2Cl_2, 0°C, 95%; c: t-BuLi (1 equiv), Et_2O, -70°C, 15 min then $ZnCl_2$ in Et_2O (1 equiv), 60 min; d: Et_2O, 24°C,15h, 73%; e: Me_3Al-$TMOSO_2CF_3$ (1:1, 2 equiv), CH_2Cl_2, 0°C, 60 min, 95%; f: same as **9** → **5** in Scheme I.

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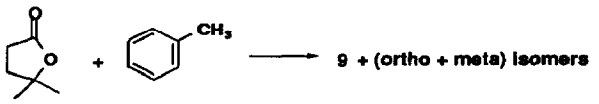
10. Our initial attempt to generate **9** by the Fridel-Crafts condensation of lactone **21** and toluene gave an inseparable mixture of ortho, metha and para isomers.



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