Synthèse totale d'acides aminés
Utilisant la (-)-menthone comme auxiliaire chiral

Projet réalisé par
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Dans le cadre du stage T3

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Dans le cadre de ce stage, il m'a été confié d'effectuer la synthèse d'acides aminés en seulement quelques étapes. On sait que dans le monde de la recherche, les acides aminés sont des sujets les plus convoités. Ici dans cette synthèse on pourra observer la concrétisation d'un acide aminé, le 2-(9H-Fluorèn-9-ylméthoxycarbonylamino)-2-méthyl-heptanoic acide en seulement 7 étapes.
Partie expérimentale

Carboalumination Alcohol

The reaction has to be strictly anhydrous. The zirconium catalyst was put into solution in CH₂Cl₂ and purged 3 times with argon. The AlMe₃ was added with precaution at rt. After 5-10 min of stirring, the solution was cooled to 0 ºC and the CH₂Cl₂/heptyne solution (0.506 mL heptyne 1.3 eq. 1.93 mL CH₂Cl₂ [2.0 M]) was added dropwise. There was CH₄ emanation and the solution turned dark yellow. It was stirred over night at rt.

The previous mixture was cooled down at -30 ºC. The aldehyde diluted in THF is add to the cooled mixture (slowly) and let it go to r.1, Follow by TLC. The resulting solution is quenched with saturated aqueous potassium carbonate until there is no more bubbles. There will be white solid. At ODC add a lot of HCl 1 N to dissolve the white solid The aqueous layer was separated then extracted 3X with diethyl ether. The organics layers were combined and washed with brine, dried over MgSO₄, filtered and evaporated under reduced pressure to yield a yellow oil. Purification by flash chromatography (2% ether in hexanes) gave 0.290g (58%) of a slightly yellow oil. IH NMR (CDCL₃): δ 5.34-5.31 (d, 1H, 8Hz) 4.68-4.66 (d, 1H, 8Hz), 2.21-2.16 (qd, 1H), 2.02-1.97 (t, H, Hz) 1.69-1.67 (m, H) 1.64 (s 3H), 1.44-1.39 (qt H) 1.33-1.24 (m H), 0.95-0.93 (d 3H), 0.91-0.86 (t, H) 0.90-0.87 (d, H) 0.80-0.79 (d H) MS (m/z, intensity): 3260 (M-H₂O). Exact mass calculated for C₁₉H₃₆O 280.2756±0.0008, 280 M+ found 280.9824
Azide
The Mitsunobu reaction
Dissolve the alcohol and PPH₃ in benzene at DOC [0.23 M] under argon atmosphere and stir. At r.t add slowly and simultaneously the DEAD and HN₃ and stir (It is very important to add slowly one drop of DEAD and three drop of HN₃ freshly made and titrate). Follow the reaction by TLC. To the resulting solution add hexane in excess to precipitate the OPPH₃ salts. Filtrate the solution on celite and evaporate. Add again hexane if salts still there, and filtrate until there is no more salts. Than the solution is extracted 3X with 70% MeOH/H₂O. The organics layers were combined and washed with brine, dried over MgSO₄, filtered and evaporated under reduced pressure to yield a yellow oil. (100%). For this reaction we can't purified on silica gel. The crude will be take for the next reaction.

Amine
Dissolve the azide in ether [0. 1M] under argon atmosphere at rt and stir. Add THF [0. 1M] and at DOC add slowly LiAlH₄. Than bring at r.t and stir for 3-4 days. Follow by TLC. Add LiAlH₄ if needed.. The resulting solution is quenched with sodium hydroxide IN and water at DOC until there is no more bubbles. The resulting solution is filtered and dried over MgSO₄ and evaporated under reduced pressure to yield a yellow oil. Purification by flash chromatography (5% ethyl acetate in hexanes up to 100 % ethyl acetate) gave 37mg (47%) of a slightly yellow oil. IH NMR (CDCL₃): δ 5.35-5.40 and 5.17-5.2(dd, 2H 15Hz) 3.58-3.62 ( m, 2 H) 1.71-1.84 (m, IH), 1.60-1.63 (2d broad, 3H) 1.24-1.29 (m broad, 6H), 0.84-1.03 (m, 23H).
Dissolve the amine in CH₂Cl₂ under air atmosphere at r.t. and add NaII[C03 and stir. Cool down the mixture at O°C and add the 9-fluorenylmethyl chloroformate in CH₂Cl₂ solution and stir at r.t for lh30. Separate the organic layer. The organics layers were combined and washed with brine, dried over MgSO₄, filtered and evaporated under reduced pressure to yield a yellow. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 100mg (40%) of a slightly yellow oil. IH NMR (CDCl₃): 7.60-7.63 (d, IH 8 Hz) 7.76-7.78 (d IH 8 Hz), 7.32-7.38 (td, 6H, 9 Hz) 5.21-5.44 (2d broad, 2H), 4.75 (s broad, 2H), 4.36 (s broad, IH) 4.21-4.26 (t, 2H 7Hz) 1.71.84 (m, IH), 1.60-1.63 (2d broad, 3H) 1.24-1.29 (m broad, 6H), 0.84-1.03 (m, 22H).

Amide
Dissolve the amine in acetone at -78°C and put ozone (gas) in the solution until the blue coloration. Than add the Jones's reagent until the green coloration disappears and the orange coloration appear. Let stir the reaction for 1 hour at rt add isobutanol and evaporate the solution under reduced pressure. Add water and extract with CH₂Cl₂ 4X. Evaporate the solution under reduced pressure and extract with diethyl ether and sodium hydroxide 4X. The organics layers were combined and washed with brine, dried over MgSO₄, filtered and evaporated under reduced pressure to yield a yellow oil. Purification by prep. chromatography gave 47mg (88%) of a slightly yellow oil. IH NMR (CDCl₃) N/D (ordinateur pour RMNIH non disponible)
La synthèse s'est déroulée sans problèmes majeurs. Il ne reste qu'à obtenir une meilleure selectivité pour la réaction de Mitsunobu. Plusieurs essais ont été fait et plusieurs restent à faire pour améliorer les « ee » de cette réaction. De plus, la réaction avec LiAlH4 est un peu longue, elle dure environ 3-4 jours. Ici aussi il y aura de l'amélioration à apporter. On ne peut ici conclure définitivement cette synthèse puisqu'elle n'est pas tout à fait terminée. Stephane y travaille. Pour le résultat final ainsi que la conclusion complète de cette synthèse on pourra consulter son rapport.

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